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THE UNIVERSITY OF ALBERTA

STRUCTURAL AND SYNTHETIC STUDIES  
ON SOME LYCOPODIUM ALKALOIDS

by

John Kenneth Jenkins



A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

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THE REQUIREMENTS FOR THE DEGREE OF

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DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FEBRUARY, 1968



UNIVERSITY OF ALBERTA  
FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read,  
and recommend to the Faculty of Graduate Studies  
for acceptance, a thesis entitled "Structural and  
Synthetic Studies on Some Lycopodium Alkaloids",  
submitted by John Kenneth Jenkins, B.Sc.(Hon.)  
in partial fulfilment of the requirements for the  
degree of Doctor of Philosophy.



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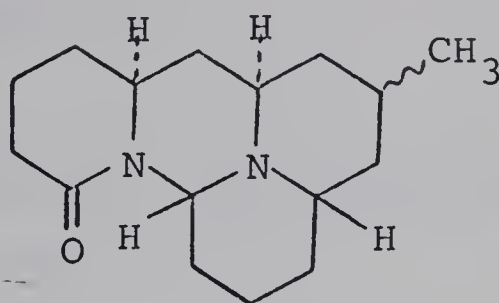
Mrs. Freda Penny for the typing of this manuscript.





## ABSTRACT

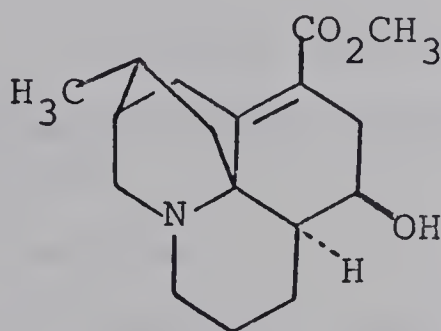
Cernuine and the minor alkaloids, from Lycopodium cernuum, have been reexamined. The structure and stereochemistry of cernuine (I),



I

has been determined. The biosynthesis of cernuine is discussed.

Some simple chemical transformations of annopodine have been carried out and are interpreted in light of its structure (II) as determined by



II

X-ray diffraction studies. Possible biosynthetic routes leading to annopodine are proposed.

The synthesis of luciduline, an alkaloid from Lycopodium lucidulum, has been attempted.



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## INTRODUCTION

Since the time of Bodeker<sup>1</sup>, who in 1881 isolated an alkaloid from Lycopodium complanatum L. which he called lycopodine, more than one hundred alkaloids have been isolated from the Lycopodium family. To date nineteen Lycopodium species have been investigated, while there are greater than two hundred species described<sup>11</sup>.

Table 1 lists, in order of increasing C, H and N content, the alkaloids isolated to date. Not all their structures have been elucidated nor have all of them been completely characterized. The various Lycopodium species (Table 2) from which a particular alkaloid has been isolated is noted in column three. The column headed, structural type, refers to a typical example of the group of Lycopodium alkaloids which has a similar structure. The references refer to the isolation and, in some cases, to the elucidation of the structure of the particular alkaloid.



TABLE 1

Mol. Formula	Name	Occurrence	M.P. °C	St. Type	References
$C_{10}H_{14}N_2$	nicotine	2,4,5,7,11, 13,19,15	226 picrate	a	2,3,4,5,6,7,8
$C_{10}H_{19}N$	saururine	16	244 B.CH <sub>3</sub> I		9
$C_{10}H_{19-21}NO$		2	290 B.CH <sub>3</sub> I		10
$C_{11}H_{19}NO$	L.18	5	195 picrate		12
$C_{11}H_{19}NO_2$	serratanine	18	239-41 B.HClO <sub>4</sub>		62
$C_{13}H_{21}NO$	L.21, luciduline	11	201 B.HClO <sub>4</sub>		5,61
$C_{14}H_{21}NO$	L.35	8	133		13
$C_{15}H_{18}N_2O$	selagine	17	224-6	b	14
$C_{15}H_{20}N_2O$	pillijanine	16	64-5		15





TABLE 1 contd.

Mol. formula	Name	Occurrence	M.P. °C	St. Type	References
$C_{15}H_{25}NO$	L.26	15	171		7
$C_{16}H_{21}NO_3$	annotinine, L.7	2,3	232	c	16,10,17
$C_{16}H_{21}NO_3$	annotine, L.11	2,5,17	175	d	16,18,10, 19
$C_{16}H_{21}NO_3$	Base VIII	2	216 B.CH <sub>3</sub> I		2
$C_{16}H_{22}N_2$	lycodine	2,5,13,9,12, 18	118-9	k	20,21,22,23, 24
$C_{16}H_{23}NO$	fawcettidine, (Base F)		223-5 B.CH <sub>3</sub> I	g	26,27
$C_{16}H_{23}NO$	anhydroly- codoline	1	274-6 B.HCl dec.	f	28
$C_{16}H_{23}NO_2$	acrifoline, L.27	2,3,5,17	97-104	f	10,2,17,29
$C_{16}H_{23}NO_2$	L.29, Base VI	2,3	274 B.HClO <sub>4</sub>		17,2



TABLE I contd.

Mol. Formula	Name	Occurrence	M.P. °C	St. Type	References
$C_{16}H_{24}N_2O$	des-N-methyl- $\alpha$ -obscurine	5, 9	270-2	k	30, 23, 22, 55
$C_{16}H_{24}N_2O_2$	hydroxy-des-N-methyl- $\alpha$ -obscurine	7		k	31
$C_{16}H_{24}N_2O_2$	Base R	9	129-30		
$C_{16}H_{25}N$	anhydrodi-hydrolycopodine, L.14	19	238 B.HClO <sub>4</sub>	f	8, 32
$C_{16}H_{25}NO$		2	261 B.CH <sub>3</sub> I		10
$C_{16}H_{25}NO$	L.24	11	278 B.HClO <sub>4</sub>		5
$C_{16}H_{25}NO$	L.16	13	221 B.HClO <sub>4</sub>		6
$C_{16}H_{25}NO$	L.13, isolycopodine	2, 5, 11, 13, 15, 19	136		18, 2, 12, 5, 7, 8



TABLE 1 contd.

Mol. Formula	Name	Occurrence	M.P. °C	St. Type	References
$C_{16}H_{25}NO$	lycopodine	2, 3, 5, 6, 7, 8, 1, 11, 13, 15, 17, 14, 19, 10	116	f	13, 28, 5, 22, 6, 7, 29, 8, 33, 16, 10, 17, 12, 58, 25, 4
$C_{16}H_{25}NO_2$	L.9 (lycopodine and o-acetyllofoline	2	122	f	16
$C_{16}H_{25}NO_2$	6- $\alpha$ -hydroxylycopodine, L.20	11	259	f	5, 36
$C_{16}H_{25}NO_2$	$\psi$ -sela-gine, L.23	11, 17	161-2		5, 29
$C_{16}H_{25}NO_2$	L.25	11	297 B.HClO <sub>4</sub>		5
$C_{16}H_{25}NO_2$	lycofoline	2	142	f	37
$C_{16}H_{25}NO_2$	lycodo-line, L.8, L.30	2, 3, 5, 1, 9, 11, 17, 14, 18	180	f	16, 17, 22, 28, 26, 29, 33, 39, 64



TABLE 1 contd.

Mol. Formula	Name	Occurrence	M.P. °C	St. Type	Reference
$C_{16}H_{25}NO_2$	diol I	6	261-3		34
$C_{16}H_{25}NO_2$	debenzoy- lalopecurine	1	230-2		28
$C_{16}H_{25}NO_2$	clavatine	2	212-3	f	40, 2
$C_{16}H_{25}NO_2$	clavolone, L.34	5, 6, 8, 1, 10	241	f	14, 58, 25, 13, 28
$C_{16}H_{25}NO_2$	annofoline	2	156-7	f	37
$C_{16}H_{25}NO_2$	fawcettine, Base A	9, 10	241 B.CH <sub>3</sub> I	g	25, 26, 23, 42
$C_{16}H_{25}NO_2$	flabel- liformine, clavatine	5, 6, 7	212	f	43, 34, 44
$C_{16}H_{25}NO_3$	alopecuridine	1	171-2		28





TABLE 1 contd.

Mol. Formula	Name	Occurrence	M.P. °C	St. Type	References
$C_{16}H_{25}NO_3$	serratine	18	253	e	39, 45
$C_{16}H_{25}NO_3$	serratinine	18	244-5	e	39
$C_{16}H_{25-27}NO_2$		6	261-3		58
$C_{16}H_{26}N_2O$	cernuine, L.32	4	106	h	3, 46
$C_{16}H_{26}N_2O_2$	lycocer- nuine, L.33	4	225	h	3, 46
$C_{16}H_{27}N$	L.4	7	225 B.HClO <sub>4</sub>		4
$C_{16}H_{27}NO$	L.22	11	108		5
$C_{16}H_{27}NO$	L.10	2	223 B.HClO <sub>4</sub>		16
$C_{16}H_{27}NO$	dihydro- lycopodine, L.1, com- planatine	5, 6, 7, 10	168	f	25, 4, 58



TABLE I contd.

Mol. Formula	Name	Occurrence	M.P. °C	St. Type	References
$C_{16}H_{27}NO_2$	deacetyl fawcettine	9, 10	203-4	f	25, 26
$C_{16}H_{28}N_2$	dihydrodeoxycernuine	4	64-5	h	46
$C_{17}H_{24}N_2$	N-methyllycodine	7	91-2	k	55, 66, 21
$C_{17}H_{24}N_2O$	$\beta$ -obscurine	2, 7, 13, 12	317-8	k	4, 47, 6, 55
$C_{17}H_{25}NO_2$	Base E	9	267 B.HClO <sub>4</sub>		26
$C_{17}H_{25}NO_2$	Base IX	2	324 B.CH <sub>3</sub> I		2
$C_{17}H_{25}NO_3$	annopodine	2	212	i	48, 50, 51
$C_{17}H_{25}NO_3$	lyconnotine	2	123	j	52, 49
$C_{17}H_{25}NO_3$	Base X	2	315 B.CH <sub>3</sub> I		2



TABLE 1 contd.

Mol. Formula	Name	Occurrence	M.P. °C	St. Type	References
$C_{17}H_{26}N_2O$	sauroxine	17	198	k	9, 54
$C_{17}H_{26}N_2O$	$\alpha$ -obscu- rine	2, 5, 7, 13, 12	282-3	k	4, 47, 55, 6
$C_{17}H_{27}NO_2$	L.28, Base V	2, 3	211 B.HClO <sub>4</sub>		2, 17
$C_{17}H_{27}NO_2$	clavatoxine	5	185-6		43
$C_{17}H_{32}N_2O_2$ ?	Base 278I	4			50
$C_{17}H_{32}N_2O_2$ ?	Base 278K	4			50
$C_{18}H_{25}NO_3$	O-acetyla- crifoline, L.12	2	119	f	16, 56
$C_{18}H_{25}NO_3$	Base XI	2	272 B.CH <sub>3</sub> I		
$C_{18}H_{25}NO_4$	Base XII	2	283 B.CH <sub>3</sub> I		2



TABLE 1. contd.

Mol. Formula	Name	Occurrence	M.P. °C	St. Type	References
$C_{18}H_{27}NO_2$	5-acetyllycofoline, Base M	9	280-2 B.HCl 0.4	f	38
$C_{18}H_{27}NO_3$	Base G	9	198-200 B.HCl 0.4		26
$C_{18}H_{27}NO_3$	L.17	13	296 B.HCl 0.4		6
$C_{18}H_{28}N_2O$	flabellidine, L.5	7	280-2 B.HCl 0.4	k	4, 31
$C_{18}H_{28}N_2O_2$	serratinidine	19	232-4	g	57
$C_{18}H_{29}NO_2$	O-acetyldihydrolycopodine, L.2	6, 7	97	f	4, 34
$C_{18}H_{29}NO_3$	lycoclavine	5, 6	212-3	f	58
$C_{18}H_{29}NO_3$	fawcettine, $\beta$ -lofoline	2, 5, 9, 10	166-7	f	38, 37, 25, 26
$C_{18}H_{29}NO_3$	lofoline, $\alpha$ -lofoline	2	211-2	f	37





TABLE 1 contd..

Mol. Formula	Name	Occurrence	M.P. °C	St. Type	References
$C_{18}H_{29}NO_4$	lycofawcine, Base L	9	290-4 B.HClO <sub>4</sub>	f	23,65
$C_{19}H_{21}NO_2$	Base 295E	4			50
$C_{20}H_{21}NO_5$	Base O, ace- tyllycofaw- cine	9	181-2	f	38,65
$C_{20}H_{29}NO_4$	lycofoline diacetate, Base N	9	140	f	38
$C_{20}H_{29}NO_4$	L.31, Base VII	2,3	217 B.HClO <sub>4</sub>		2,17
$C_{20}H_{31}NO_4$ ?	L.15	19	231 B.HClO <sub>4</sub>		8
$C_{20}H_{31}NO_4$	O-acetyllo- foline	2	272-3 dec. B.HClO <sub>4</sub>	f	16,35
$C_{20}H_{31}NO_4$	O-acetyl- fawcettine, Base K	9	117	f	38



TABLE 1 contd.

Mol. Formula	Name	Occurrence	M.P. °C	St. Type	References
$C_{20}H_{31}NO_4$	O-acetyllly-coclavine	6	144-5	f	58
$C_{21}H_{26}N_2O_3$	Base 354H	4	145-7		50
$C_{21}H_{27}NO$	Base 309F	4			50
$C_{23}H_{27-29}NO_4$	Base 253	1	253		60
$C_{23}H_{29}NO_3$	alopecurine	1	244-5		28
$C_{32}H_{44}N_2O_5$	annotoxine, L.11 + L.27	2,5	197		10
$C_{32}H_{52}NO_3$	Complex (L.1 and flabelliformine)	5,6,7	208	f	58
$C_{18}H_{28}N_2O$	flabelline	7	185-187.5	1	59

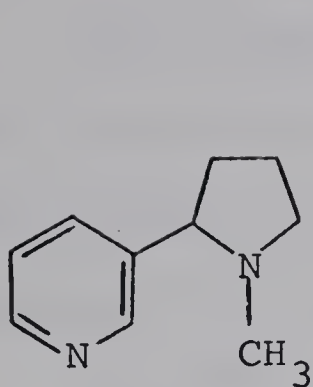


TABLE 2

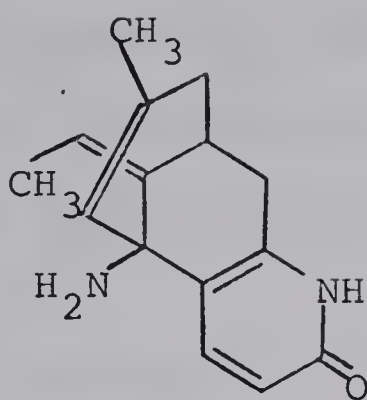
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2.     L. annotinum   Linn.
3.     L. annotinum   var acrifolium   Fern.
4.     L. cernuum   Linn.
5.     L. clavatum   Linn.
6.     L. clavatum   var megastachyon Fern.et Bissel.
7.     L. complanatum   Linn. (L. flabelliforme Fern.)
8.     L. densum   Labill.
9.     L. fawcettii   Lloyd et Underwood.
10.    L. clavatum   (Jamaica).
11.    L. lucidulum   Michx.
12.    L. obscurum   Linn.
13.    L. obscurum   var dendroideum
14.    L. phlegmaria   Linn.
15.    L. sabinaefolium   Willd.
16.    L. saururas   Lam.
17.    L. selago   Linn.
18.    L. serratum Thunb.   var Thunbergii Makino,
19.    L. tristachyum   Pursh.



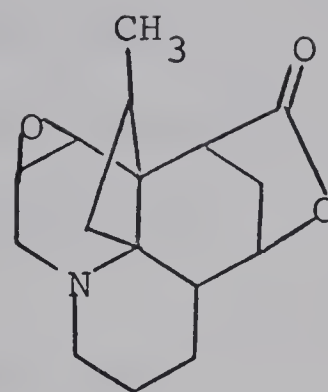
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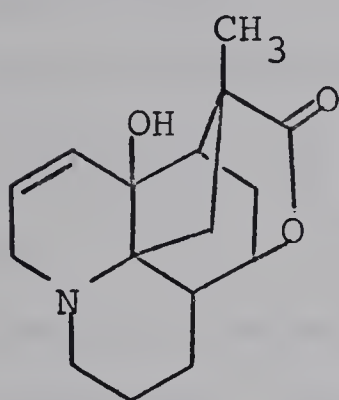
a. nicotine



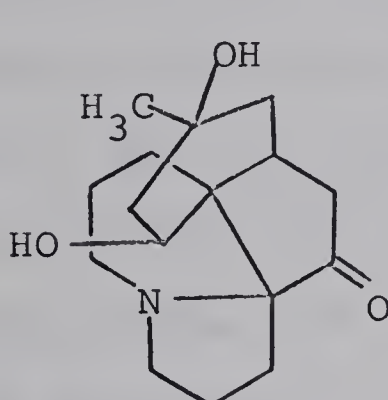
b. selagine



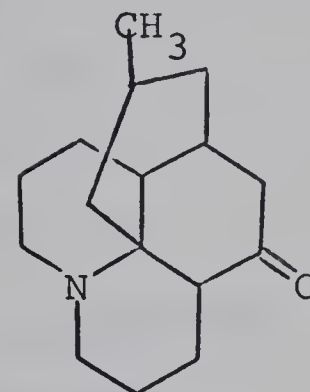
c. annotinine



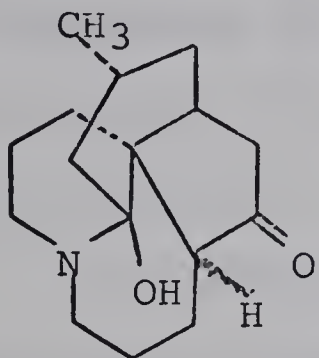
d. annotine



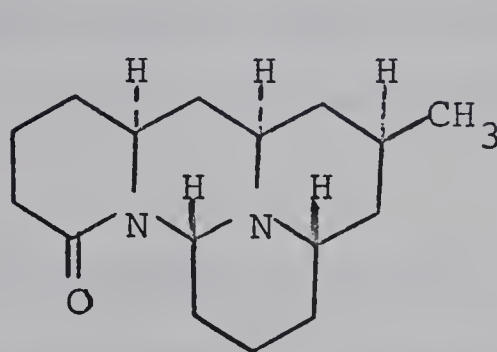
e. serratine



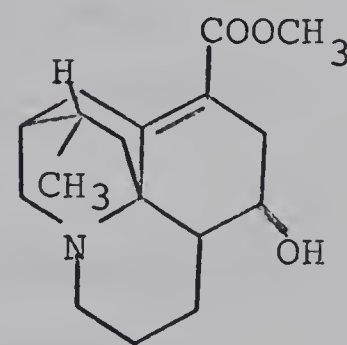
f. lycopodine



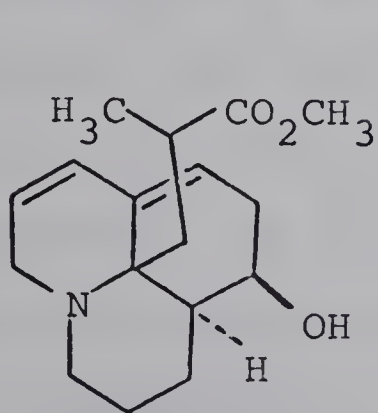
g. fawcettimine



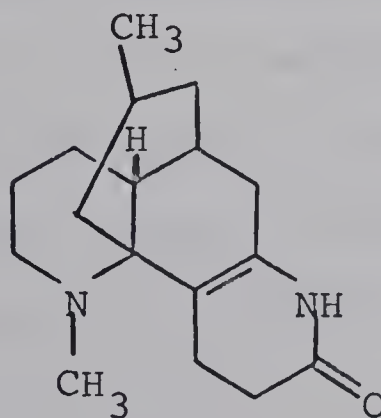
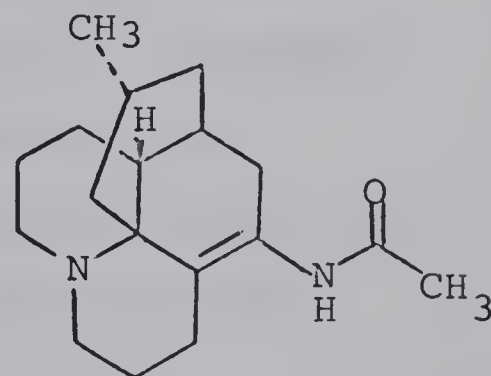
h. cernuine



i. annopodine



j. lyconnotine

k.  $\alpha$ -obscurine

l. flabelline



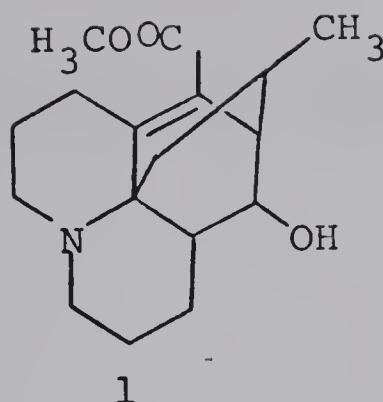


This thesis describes work which has led to the elucidation of the structures of cernuine and annopodine as well as work directed towards the synthesis of luciduline.

In 1942 Marion and Manske<sup>4</sup> isolated from L.cernuum L. nicotine and two crystalline alkaloids. They called the major alkaloid L.32 or cernuine,  $C_{16}H_{26}N_2O$ , mp  $106^\circ$ , and the minor one L.33, mp  $218^\circ$ . The fact that this plant did not seem to contain any of the more common Lycopodium alkaloids, and the fact that an early spectroscopic examination indicated that the two crystalline alkaloids did not possess the usual lycopodine skeleton led us to investigate in detail this species.

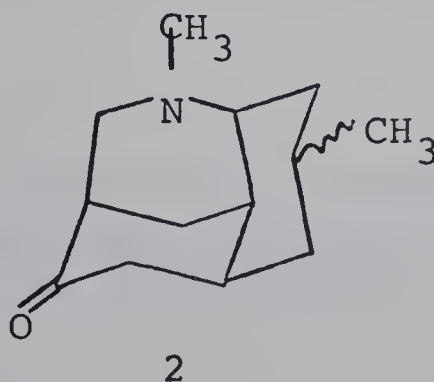
The second section deals with the investigation of a minor alkaloid, isolated<sup>48</sup> from Lycopodium annotinum L. and named annopodine,  $C_{17}H_{25}NO_3$ . Earlier investigations in this laboratory<sup>48</sup> indicated that this alkaloid had the usual julolidine type skeleton. At that time, based on evidence accumulated, the following structure 1 was tentatively proposed for annopodine.





If this structure were correct this alkaloid would represent a new type of Lycopodium alkaloid. In an attempt to confirm this hypothesis, further chemical and physical studies were carried out.

The third section of this thesis deals with an attempted synthesis of the alkaloid luciduline,  $C_{13}H_{21}NO$ , isolated<sup>61</sup> from Lycopodium lucidulum Michx. This alkaloid is thought to be identical with L.21,  $C_{13}H_{21}NO$ , isolated by Marion and Manske<sup>5</sup> in 1946. Degradation studies in this laboratory<sup>61</sup> indicated that luciduline has the following structure 2,



and in order to confirm this, the synthesis was undertaken.



## DISCUSSION AND RESULTS

## SECTION ONE

The alkaloids of Lycopodium cernuum L., a plant indigenous to the tropical and sub-tropical climates<sup>81</sup>, was first investigated by Manske and Marion<sup>4</sup>. They isolated a trace of nicotine, an alkaloid which they called L.32 or cernuine mp 106°, which analyzed for  $C_{16}H_{26}N_2O$ , and another which they called L.33, mp 218°. From 9.1 Kg of dried plant material collected in Trinidad and Hawaii, Marion and Manske isolated 0.2g of cernuine and a few milligrams of L.33.

Investigations in this laboratory were carried out on the basic extracts of L. cernuum collected in Venezuela, Florida and Mexico. The major alkaloid present was found to be identical<sup>\*</sup> with L.33,

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\* The identity of the two alkaloids was established by direct comparison with samples supplied by R.H.F. Manske.



which we have given the name lycocernuine.

The minor alkaloid was identical with cernuine.

The ratio of lycocernuine-cernuine in the various basic extracts obtained<sup>\*</sup> varied from 3:1 to 1:1.4.

No nicotine could be isolated, however it may have been present in trace amounts.

Investigation of the other basic constituents, which will be discussed later, yielded several minor alkaloids, not all of which were completely characterized. One minor alkaloid which was isolated proved to be identical with dihydro-deoxycernuine, the lithium aluminum hydride reduction product of cernuine.

The crude basic extract was obtained in the following manner. The dried, finely ground plant material was extracted with methanol, then the extracts were evaporated to a sludge which was slurried in 3% aqueous tartaric acid and the insoluble material filtered off. The filtrate

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\* Some of the crude basic extract was obtained from Smith, Kline and French Laboratories, Philadelphia (S.K.F.), while other extractions were carried out in this laboratory.





was thoroughly extracted with ether to remove neutral substances, made strongly basic with ammonium hydroxide and extracted with chloroform. Evaporation of the chloroform extracts yielded the crude alkaloidal material. Twenty-one kilograms of dried plant material, collected in Mexico, yielded 8g of crude bases from which 2.8g of lycocernuine and 1.1g of cernuine were obtained. Twenty-six grams of crude extract from S.K.F. yielded 3g of lycocernuine and 1g of cernuine, while a 9g crude alkaloidal extract, also from S.K.F., yielded 1.1g of lycocernuine and 1.56g of cernuine.

Purification of the crude alkaloidal mixture was carried out either by dissolving the total extract in hot acetone and crystallizing out the majority of the lycocernuine, then chromatographing the mother liquors over alumina, or by directly chromatographing the total crude bases over alumina.

The physical and chemical behavior of cernuine<sup>\*</sup>

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\*The investigation of the physical and chemical properties of lycocernuine and its derivatives was, for the most part carried out in this laboratory by S.Valverde-Lopez (Ph.D. Thesis, University of Alberta, 1966).



which led to the elucidation of its structure will now be described. Earlier experiments in this laboratory indicated that cernuine and lycocernuine were closely related. In fact it appeared that lycocernuine was a hydroxycernuine.

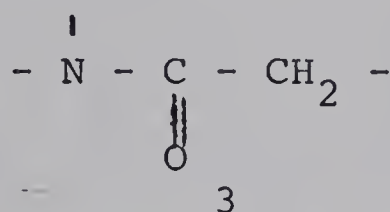
Final purification of cernuine was carried out by chromatography over alumina followed by sublimation under reduced pressure which yielded material, mp 103-104°. In our hands crystallization from Skellysolve B<sup>3</sup> could only be carried out with difficulty and yielded gummy crystals.

Mass spectral data verified the molecular formula of cernuine to be  $C_{16}H_{26}N_2O^3$ . The two nitrogens present were shown to be tertiary, one basic and one non-basic, by the following observations. Cernuine titrates as a monoacidic base [pKa' value (50% CH<sub>3</sub>OH):6.3] and forms a C<sub>17</sub> methiodide which accounts for the basic tertiary nitrogen.

The fact that the infrared spectrum shows strong absorption at 1640 cm<sup>-1</sup> (CCl<sub>4</sub>) and no NH absorption suggests the non-basic nitrogen to be present as part of an amide or lactam grouping. The 1640 cm<sup>-1</sup> band is accompanied by



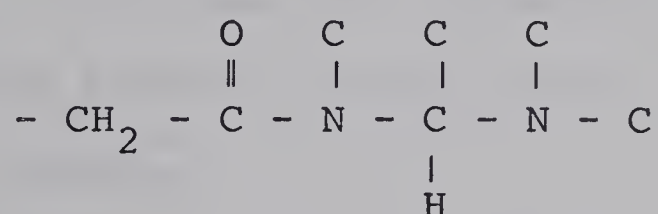
a moderately intense band at  $1415\text{ cm}^{-1}$ , which is displaced to lower frequency when the compound is treated with sodium methoxide in methanol- $\text{O-d}^{46,68}$  (two deuterium atoms are incorporated as revealed by mass spectrometry). This suggests the presence of the following grouping  $3^{69}$ .



The nuclear magnetic resonance spectrum of cernuine shows a one proton quartet at  $\tau 4.53$  ( $J=11$  &  $2.5$  cps), a series of peaks at  $\tau 6.3 - 7.1$  (3 protons), a two proton multiplet at  $\tau 7.55 - 7.80$ , and a three proton doublet at  $\tau 9.14$  ( $J=6$  cps). The doublet at  $\tau 9.14$  can readily be assigned to a secondary methyl group. The one proton quartet which appears at  $\tau 4.53$  in cernuine appears at  $\tau 4.13$  in cernuine methiodide. This indicates a HC-N- relationship between the tertiary basic nitrogen and the low field proton. When the lactam or amide grouping in cernuine is reduced, yielding dihydrodeoxycernuine the low field proton shifted to  $\tau 6.40$ . This suggests a -CO-N-CH- relationship between the non-



basic tertiary nitrogen and the low field proton. As a consequence of these two observations, the two nitrogens present in cernuine likely have a one-three relationship, with the low field proton on the carbon between them. The following partial structure 4 may now be written.



4

The resistance to catalytic reduction in neutral and acidic media as well as the fact that lithium aluminum hydride reduction gave dihydrodeoxycernuine (reduction only of a lactam or amide carbonyl as shown by mass spectrometry) indicated that the low field proton at  $\tau$ 4.53 in cernuine is not associated with an unsaturation such as C = N or C = C. The infrared spectra of dihydrodeoxycernuine showed no double bond or NH absorption.

As was pointed out in the introduction, the mass spectrum of cernuine is very different from that observed for the usual lycopodine-type alkaloids. Lycopodine, as well as those

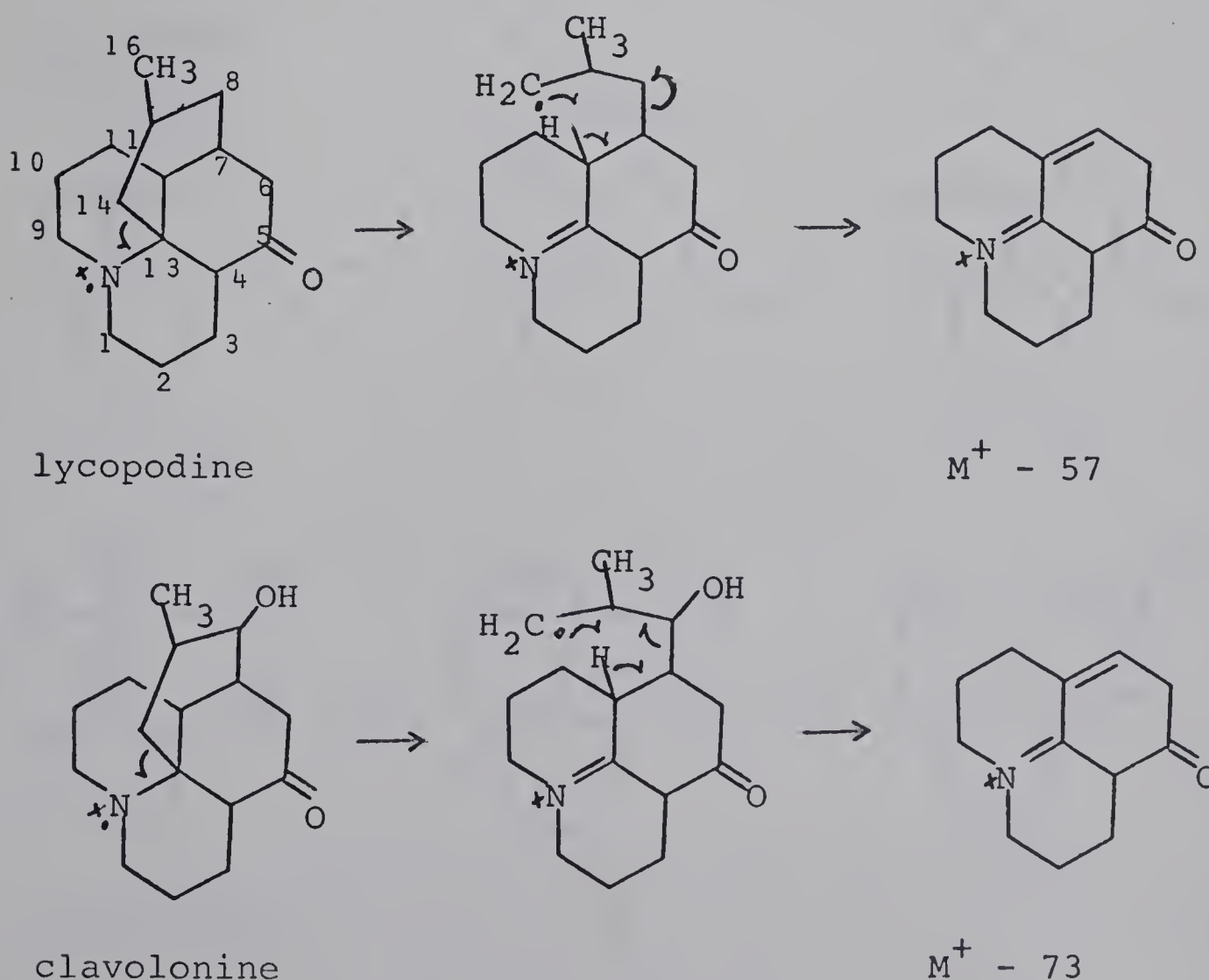




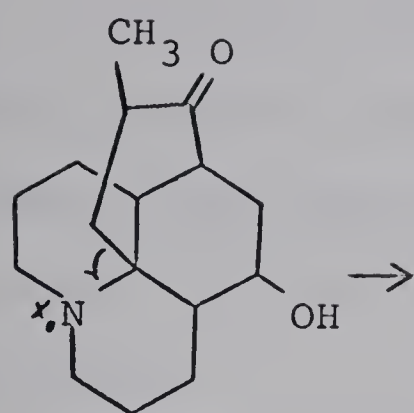
Lycopodium alkaloids<sup>70</sup> with a keto or hydroxy group on the bridge carbon (C-8), are observed to fragment first with loss of the bridging carbons. The obscurines<sup>54,70</sup> fragment in a similar fashion, as do the alkaloids such as lycodoline which are substituted at C-12.

In Scheme 1 are shown the suggested fragmentation routes which account for the higher mass fragments observed.

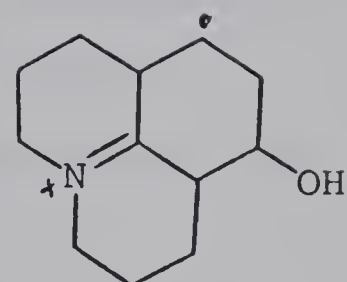
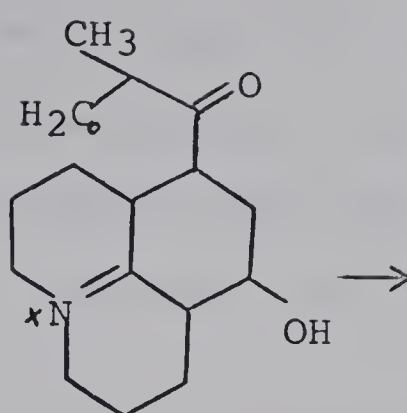
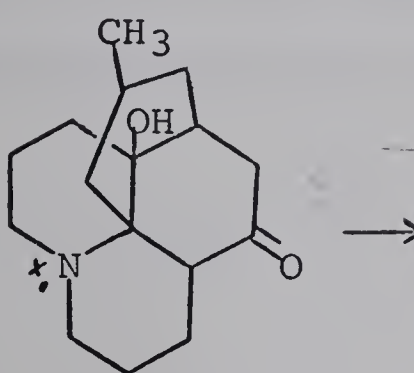
SCHEME 1



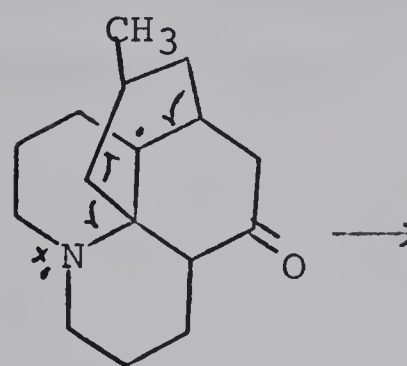
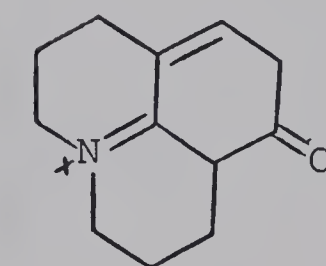
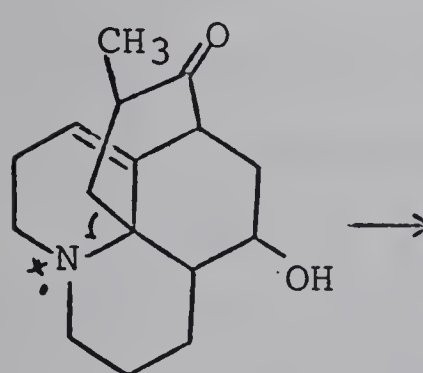




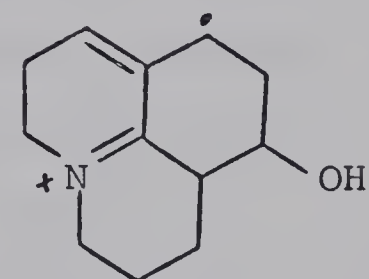
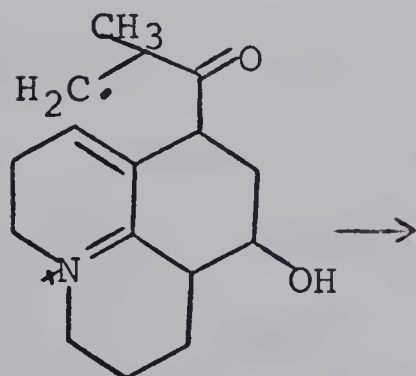
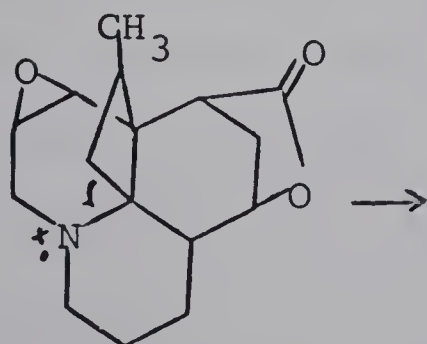
annofoline

 $M^+ - 70$ 

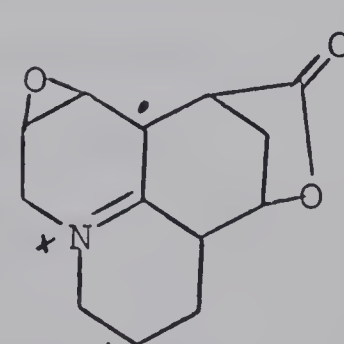
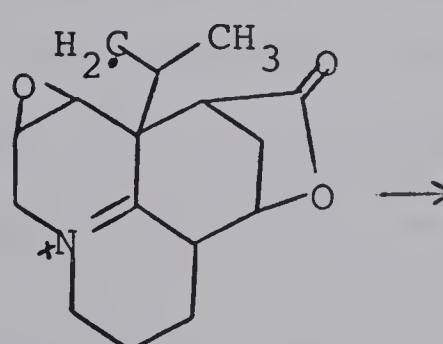
lycodoline

 $M^+ - 17$  $M^+ - 73$ 

acrifoline

 $M^+ - 70$ 

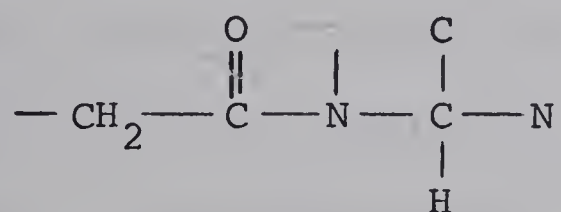
annotinine

 $M^+ - 42$

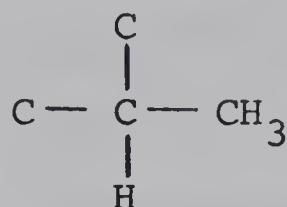


The mass spectrum of cernuine shows very intense  $M^+-29$  and  $M^+-42$  fragments which do not correspond to those of the lycopodine-type alkaloids. Thus it appeared unlikely that cernuine had a lycopodine-type skeleton.

Considering that cernuine,  $C_{16}H_{26}N_2O$ , has no unsaturations other than those mentioned and the following partial structures 4 and 5



4



5

then the molecule must be tetracyclic and the  $-\text{N}-\overset{\text{O}}{\parallel}\text{C}-$  grouping must be part of a lactam grouping.

In order to gain further information about the skeleton of cernuine it was decided to subject it to degradation. At the same time, more systematic degradations were initiated by S. Valverde-Lopez<sup>68,46</sup> on the more heavily functionalized lycocernuine, since it was felt that the two approaches would compliment one another in the final solution to the problem.

Initial dehydrogenation attempts were carried out at  $176^\circ$  using p-cymene as a solvent and Pd/C as catalyst. Short reaction time (21 hr) yielded



essentially unchanged cernuine. When a longer time (61 hr) was used the crude basic product showed a maximum at 258m $\mu$  in the ultraviolet which was shifted to 260m $\mu$  in acidic medium. The infrared spectrum (CCl<sub>4</sub>) showed intense absorption at 1665 cm<sup>-1</sup> with weaker absorption bands at 1725, 1603 and 1550 cm<sup>-1</sup>. A broad absorption band centered at 3400 cm<sup>-1</sup> was also present. Although the dehydrogenation had proceeded to some extent, under the conditions used, as evidenced by the typical pyridine absorption in the ultraviolet and the primary or secondary amide or lactam absorption in the infrared, it was decided to carry out further dehydrogenation using a higher boiling solvent.

Cernuine dissolved in tetralin with Pd/C added was dehydrogenated at 200°. The basic material isolated was chromatographed on alumina. The fraction eluted with benzene-ether showed a maximum in the ultraviolet at 262-265m $\mu$  which was shifted to 269-270m $\mu$  in acidic medium. This behavior is typical of pyridines or alkyl substituted pyridines. An examination of the thin layer chromatographic (tlc) behavior of this material on alumina showed the presence of at least twelve components, all less polar than cernuine. The separation and isolation





of the various components was not attempted. The fraction eluted with ether and chloroform contained mainly two components which were separated by preparative thin layer chromatography (ptlc) using alumina. Both components were more polar than cernuine on alumina thin layer plates.

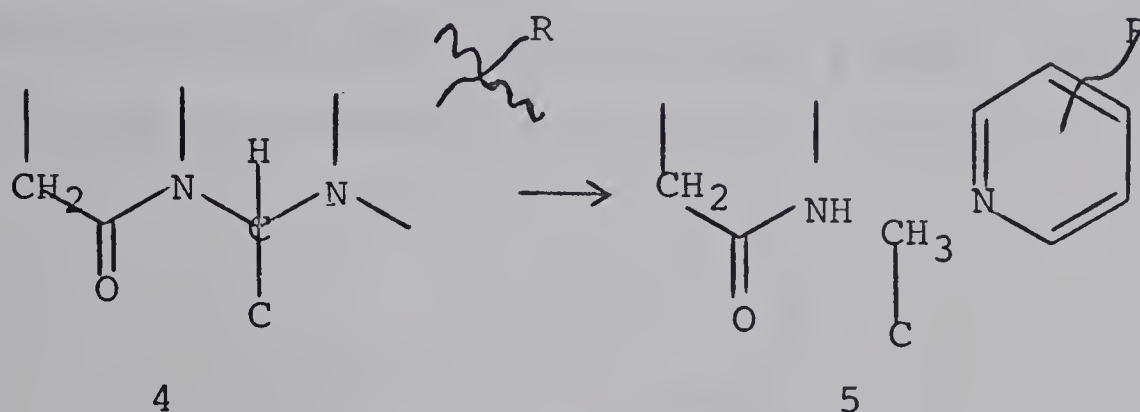
The less polar component (homogeneous according to tlc behavior) had a typical pyridine-type ultraviolet spectrum with a maximum at 262m $\mu$  which shifted to 268m $\mu$  in acidic medium. The mass spectrum showed a parent peak\* at m/e 260 (12). If indeed the fragment at m/e 260 is the molecular ion, and a pyridine has been formed in the dehydrogenation, then the conclusion may be drawn that two bonds must have been cleaved [ three unsaturations introduced (-6H); two bonds cleaved (+4H) = 262 $\rightarrow$ 260 ]. The infrared spectrum (CCl<sub>4</sub>) of this substance showed strong absorption centered at 1655cm<sup>-1</sup> with medium intensity absorption at 1660cm<sup>-1</sup>. Peaks were also present at 3390, 3300, 3200 and 3040cm<sup>-1</sup>. This data, considering the partial structures we

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\* Figures in brackets represent the intensity of a peak as a percentage of the base peak.



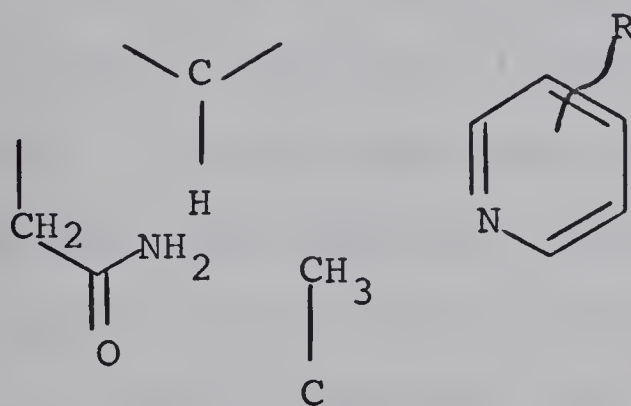
have already deduced, may be interpreted as seen in partial structure 5 with the band at  $1655\text{cm}^{-1}$  representing the lactam carbonyl and that at  $1660\text{cm}^{-1}$ , the pyridine ring.



The more polar component was also homogeneous according to its tlc behaviour. Its infrared spectrum showed sharp absorption at  $3460$  and  $3180\text{cm}^{-1}$ , indicative of non-bonded and bonded NH, weak absorption at  $3050\text{cm}^{-1}$ , a strong absorption band at  $1663\text{cm}^{-1}$ , two bands of medium intensity at  $1620$  and  $1605\text{cm}^{-1}$  and a weak band at  $1560\text{cm}^{-1}$ . The ultraviolet spectrum showed a maximum at  $264\text{m}\mu$  ( $\epsilon$  4300) which in acidic medium shifted to  $265\text{m}\mu$  ( $\epsilon$  7800). The mass spectrum of this substance showed what appeared to be a parent peak at  $m/e$  262(1).



The infrared spectrum of this dehydrogenation product resembles that of a primary amide with the amide I band at  $1663\text{cm}^{-1}$  and the amide II band at  $1605\text{cm}^{-1}$ . If the assumptions made for the previous dehydrogenation product are correct, then the spectral evidence here can be interpreted to mean that cleavage of another C-N bond has taken place. The following partial structure 6 can now be written.



6

The complexity of the two dehydrogenation products isolated indicated that if cernuine were to be degraded to a simple alkyl substituted pyridine, it would be necessary to treat it more vigorously. Cernuine was thus heated at  $300^{\circ}$  with Pd/C in tetralin in a sealed tube. The basic material obtained from the reaction mixture was purified by preparative thin layer chromatography over alumina. The less polar material, which



contained mainly two components, was purified further as described below. The more polar components were not investigated further since tlc indicated a very complicated mixture.

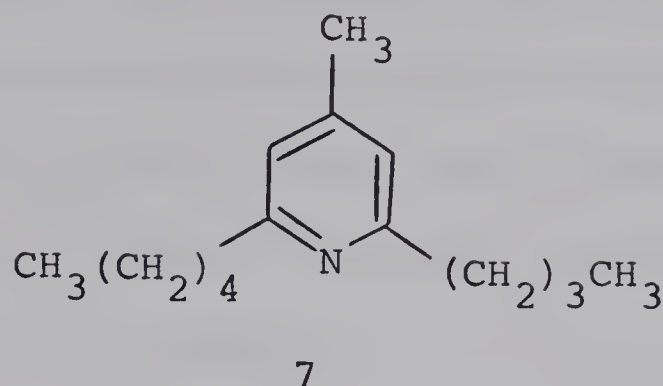
Product A, the less polar of the two less polar dehydrogenation products, was not identified. It was homogeneous on tlc (alumina and silica gel). The ultraviolet spectrum displayed a maximum at 272  $m\mu$  ( $\epsilon$ 1340) with a broad shoulder from 268 to 247  $m\mu$  ( $\epsilon$ 1260). In acidic medium the spectrum showed maxima at 297  $m\mu$  ( $\epsilon$ 1260) and 275  $m\mu$  ( $\epsilon$ 1900) with a shoulder at 248  $m\mu$  ( $\epsilon$ 950). The infrared spectrum, in agreement with the ultraviolet spectrum, showed characteristic pyridine absorption with weak absorption from 3080 to 3030  $cm^{-1}$  and strong absorption at 1595  $cm^{-1}$ . The spectrum showed no NH or OH absorption. The mass spectrum showed the ion of highest mass at  $m/e$  231(6). The nuclear magnetic resonance spectrum could not be readily interpreted in terms of the other data. It showed resonance peaks in the chemical shift region typical of  $\alpha$ ,  $\beta$  and  $\gamma$  hydrogens on a pyridine ring<sup>71</sup>, of "benzylic" hydrogens, of two different methyl groups on a pyridine ring, and of more than one terminal methyl group.

Dehydrogenation product B was identified as 2-n-





butyl-4-methyl-6-n-pentylpyridine (7) in the following manner.

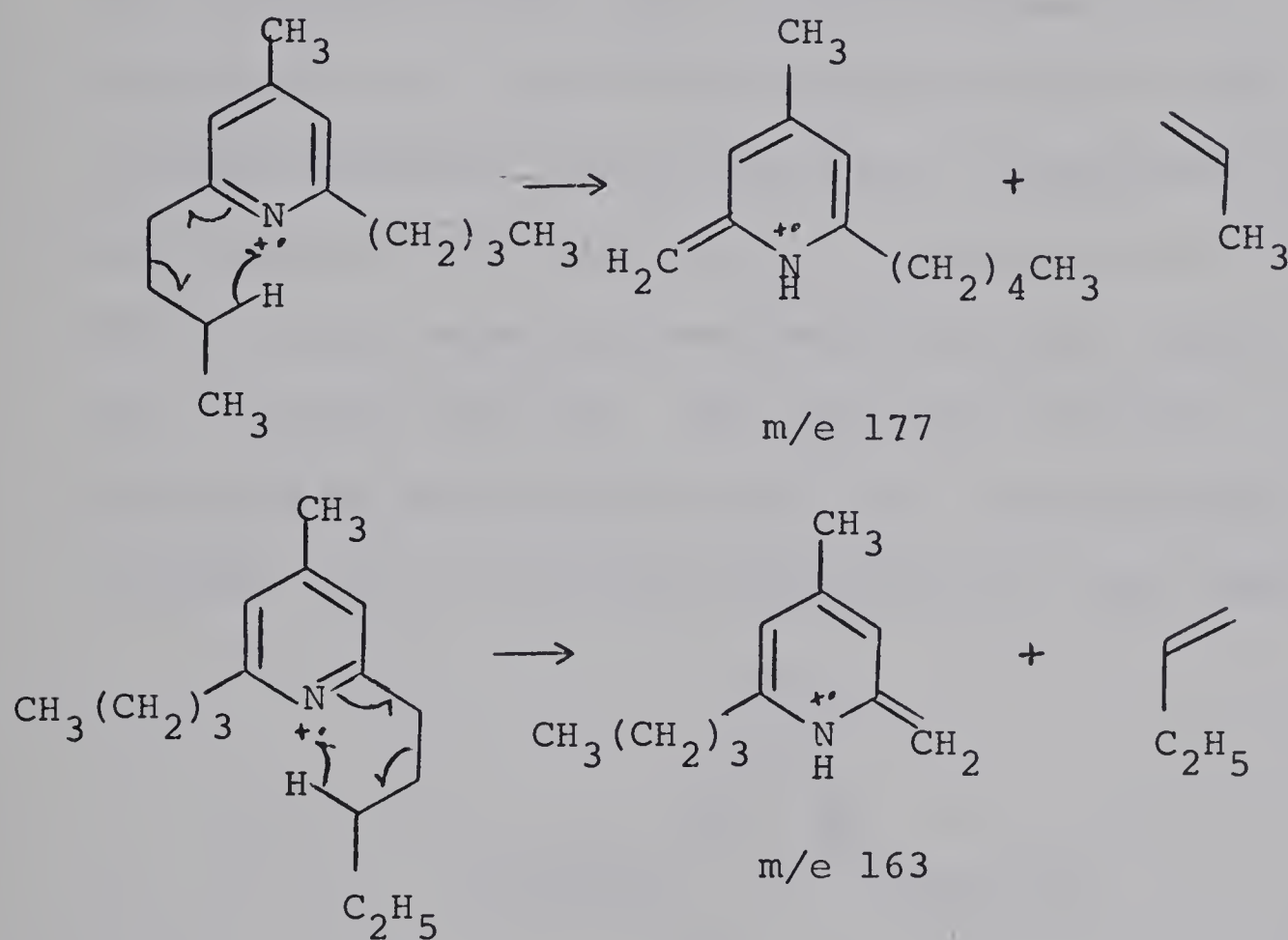


The mass spectrum showed a molecular ion at  $m/e$  219(3) (which is consistent with molecular formula  $C_{15}H_{25}N$ ). Major fragments were observed at 177(61) and 163(100). The ultraviolet spectrum, which was almost identical with that of 2,4,6-trimethylpyridine, showed maxima at 271, 268 and 264 $m\mu$ . In acidic medium only one maximum was observed at 268 $m\mu$ . The nmr spectrum showed the presence of only two hydrogens on the pyridine ring, which from their chemical shifts ( $\tau$ 3.19) must both be in the  $\beta$ -positions<sup>72</sup>. The presence of a methyl group in the  $\gamma$ -position was indicated by a three-proton signal at  $\tau$ 7.69. A four proton signal at  $\tau$ 7.22 suggested the presence of two "benzylic" methylene groups, and a complex six proton signal at  $\tau$ 9.0-9.15 indicated that the alkyl substituents in the two and six positions are not branched, i.e. either n-butyl and n-pentyl or n-propyl and n-hexyl. An examination of the fragmentation pattern observed in the mass spectrum indicated that the former is correct.



The base peak occurs at  $m/e$  163 which corresponds to the loss of butene from a pentyl side chain<sup>73</sup>. The second most intense peak occurs at  $m/e$  177 which corresponds to loss of propene from a butyl side chain. The fragmentation scheme<sup>80a</sup> is shown in Scheme 2.

SCHEME 2

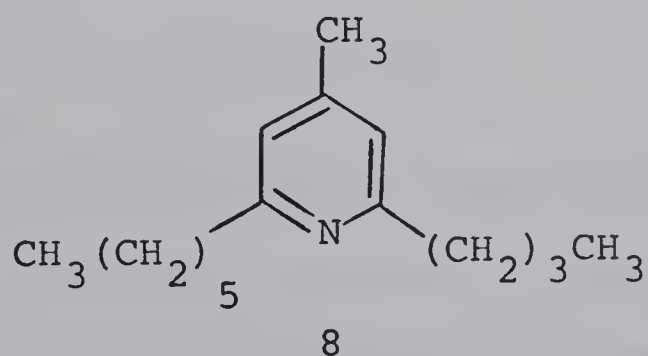


An authentic sample of 2-n-butyl-4-methyl-6-n-pentylpyridine (7) prepared by alkylation of 2-n-butyl-4-methylpyridine<sup>74</sup>, was identical (ir, uv, nmr) with the dehydrogenation product.

The pyridine 7 accounts for 15 of the 16 carbon atoms of cernuine. Since we felt that possibly the carbon atom lost during the dehydrogenation was the lactam carbonyl carbon, dihydrodeoxycernuine was



subjected to dehydrogenation in the hope of obtaining a product with all the carbon atoms present. Initial dehydrogenations carried out using similar conditions to those above yielded two major and six minor components. The mass spectrum of the crude material showed none of the desired material (another  $\text{CH}_2$  unit in one of the chains would give intense fragments at  $m/e$  163 or  $m/e$  191) so this method was abandoned in favor of a dehydrogenation using selenium. Dihydrodeoxycernuine was treated with selenium in a sealed tube at  $310^\circ$ . The volatile material was distilled under vacuum from the reaction material. The expected homologue 8 was isolated by preparative thin layer chromatography on alumina. The ultraviolet spectrum of 8 was almost



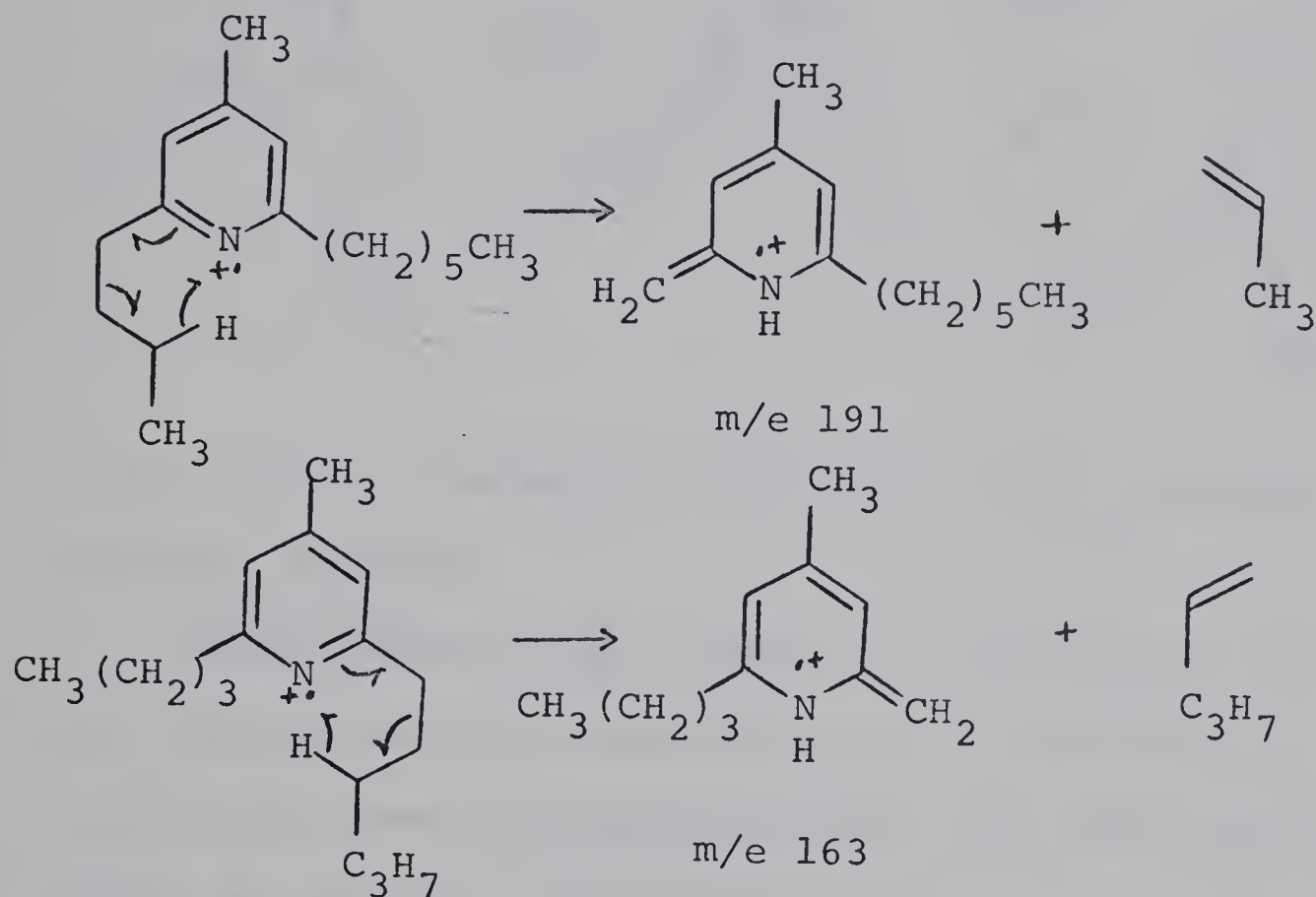
identical with that of 7, it showed a maximum at  $264\text{m}\mu$  with shoulders at  $267$  and  $271\text{m}\mu$ . In acidic medium a single band at  $269\text{m}\mu$  was observed.

The mass spectrum of this pyridine showed a molecular ion at  $m/e$  233(3), consistent with  $\text{C}_{16}\text{H}_{27}\text{N}$ , and major fragment at  $m/e$  163(100). The base peak appears at  $m/e$  163 which corresponds to loss of a



pentene unit from a hexyl side chain, while the peak associated with the loss of the other side chain has now shifted to  $m/e$  191. These fragmentation modes are represented below.

SCHEME 3



Since insufficient material was available for a nmr spectrum, it was not possible to show conclusively that the hexyl chain is unbranched. However, since the peak at  $M^+-15$  in the mass spectrum of the  $C_{16}$  dehydrogenation product (%BP=15) is no more intense than the  $M^+-15$  in the  $C_{15}$  compound (%BP=15), and since the spectrum of the  $C_{16}$  compound shows an appreciable peak at  $M^+-57$  ( $m/e$  176(24)) which is not present in the spectrum of 7 and which corresponds to the loss of a

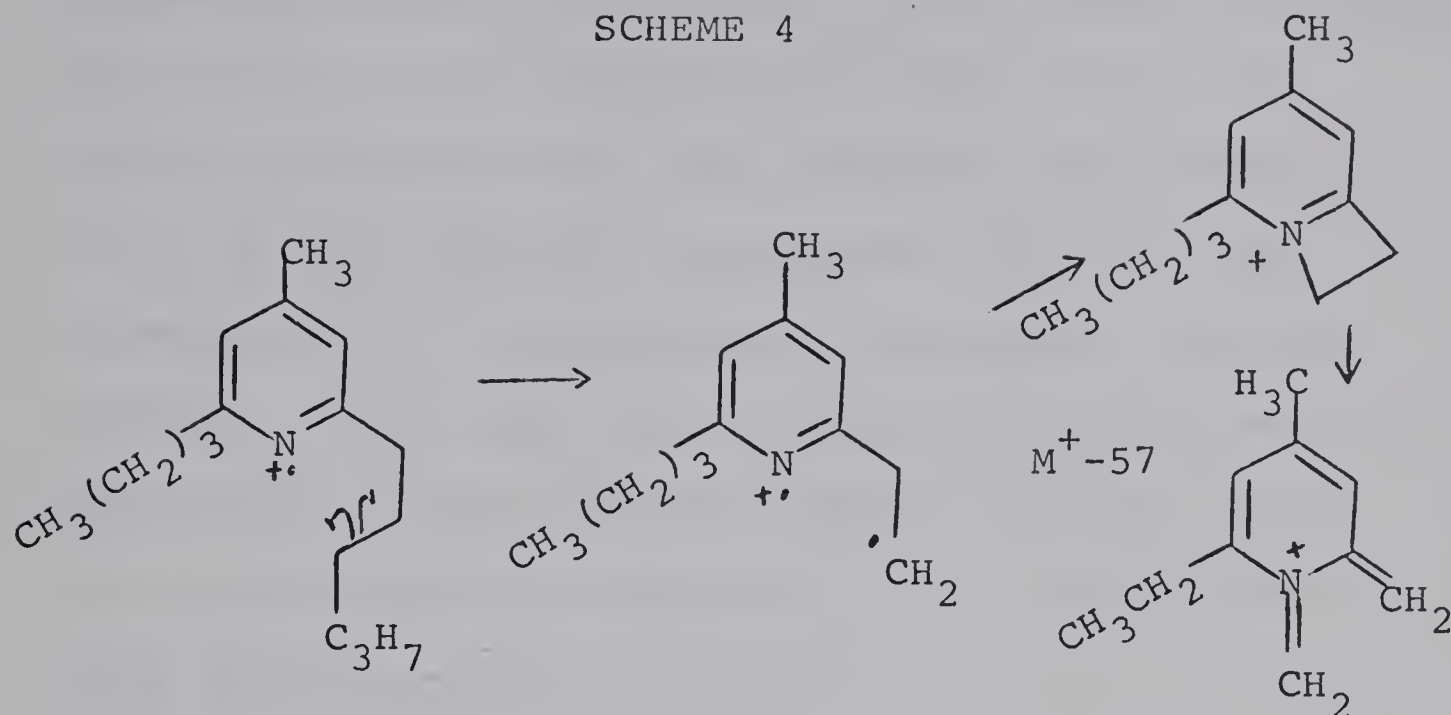






butyl radical  $^{80d}$  as shown below,

SCHEME 4

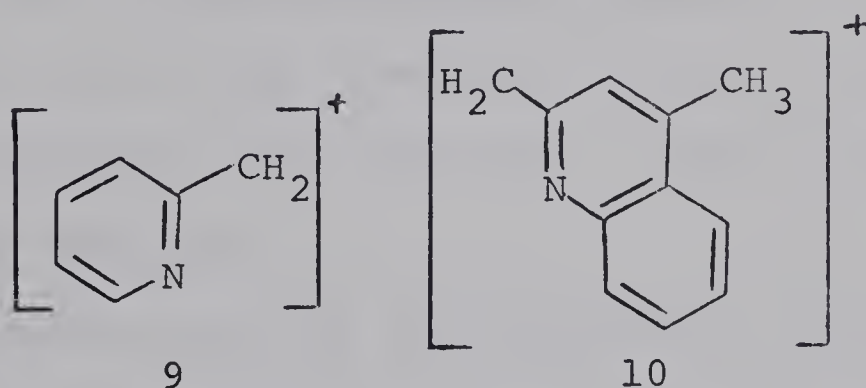


we feel that 8 correctly represents the  $C_{16}$  dehydrogenation product.

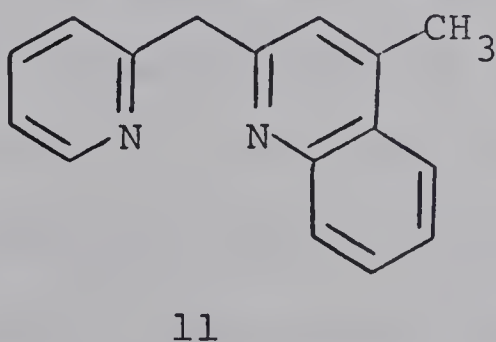
Another more polar component isolated from the same dehydrogenation was tentatively identified as 2-[ $\alpha$ -picolyl]-4-methylquinoline (11). The mass spectrum showed a molecular ion at  $m/e$  232(2) with major fragments at  $m/e$  156(100) and 92(70). The ultraviolet spectrum of the dehydrogenation product showed weak peaks at 316 and 303m $\mu$ , a medium intensity peak at 262m $\mu$  with a shoulder at 265m $\mu$ , and an intense peak at 227m $\mu$ . In acidic medium the spectrum displayed a maximum at 316m $\mu$  with a broad shoulder centered at 307m $\mu$ , at 266m $\mu$ , and a strong peak at 238m $\mu$ . In both neutral and acidic media the ultraviolet spectra of a 1:1 molar mixture of 2,4-dimethylquinoline and



$\alpha$ -picoline was found to be almost identical with that of the dehydrogenation product. The tentative structure was arrived at by considering the fact that a 1:1 mixture of the pyridine and quinoline would absorb in the uv as two isolated chromophores, thus the two chromophores in the dehydrogenation product must be isolated. This, and the fact that the molecular ion corresponds to the molecular formula  $C_{16}H_{14}N_2$ , with the two most intense fragments at m/e 156 and m/e 92 which can be written as 10 and 9.



led to the structure 11 for the



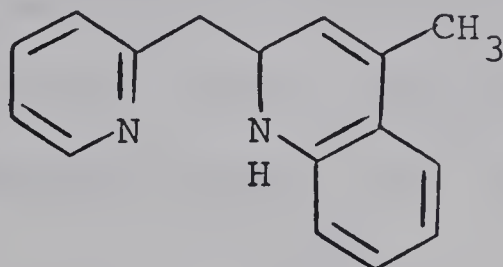
dehydrogenation product.

Attempts were made to prepare an authentic sample of 2-[ $\alpha$ -picolyl]-4-methylquinoline (11).

An attempted condensation of  $\alpha$ -picolyl lithium with 4-methylquinoline resulted in little reaction



and a good recovery of most of the unreacted 4-methylquinoline. Thin layer chromatography indicated none of the desired material had been formed. It was thought that perhaps one of the minor products might be the dihydro condensation product 12.



12

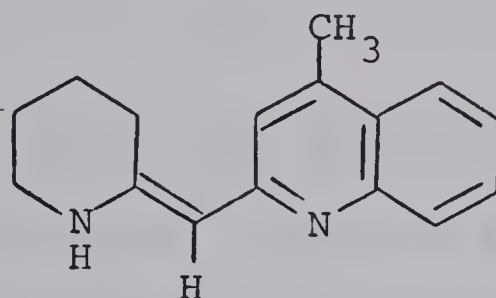
Treatment with dichlorodicyano-p-quinone<sup>75</sup> to effect oxidation to the fully aromatic structure resulted in the DDQ complexing with the base to form a black intractable material.

The condensation of 2-lithiomethyl-4-methylquinoline with pyridine was also attempted. The quinoline was again recovered as well as a viscous product which was chromatographed on alumina. The ultraviolet spectra of the various fractions indicated that none of the desired product had been formed.

A third method for the preparation of the pyridine-quinoline dehydrogenation product was attempted. This involved condensing the ethyl imino ether of  $\delta$ -valerolactam, which was prepared from  $\delta$ -valerolactam and triethyloxonium fluoroborate<sup>76</sup>, with 2-lithiomethyl-4-methylquinoline. The product, which contained 2,4-dimethylquinoline, was chromat-



ographed over alumina and then repeatedly distilled. The product, obtained in 25% yield, was an oil. The thin layer chromatographic behavior of this material indicated it to be a mixture of two basic components (perhaps the two geometrical isomers) and a neutral impurity. The mass spectrum of this material showed a molecular ion at  $m/e$  238(7), consistent with  $C_{16}H_{18}N_2$ , the expected product 13. The nmr spectrum



13

showed the presence of a one proton doublet at  $\tau$  3.4 ( $J = 1$  cps), a one proton singlet at  $\tau$  5.3, and a three proton doublet at  $\tau$  7.6 ( $J = 1$  cps), indicative of the proton  $\beta$  to the nitrogen in the pyridine ring, the olefinic proton ( $\beta$ -enamino proton, normally at  $\tau$  5.0-6.3), and of the methyl group.

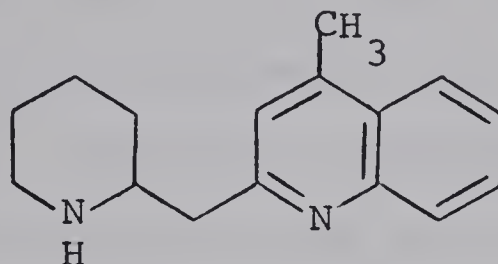
Olefin 13 was hydrogenated in methanol over Pd/C to give a product which was purified by chromatography and distillation. This product was homogeneous, as shown by its tlc behavior on alumina, and gave the expected molecular ion at  $m/e$  240 (0.2). The nmr spectrum indicated the presence of a four proton multiplet at  $\tau$  2.0 - 2.9, characteristic of the







benzene ring protons, a one proton broad singlet at  $\tau$  3.05, assigned to the  $\beta$ -proton on the pyridine ring and a three proton doublet at  $\tau$  7.45 ( $J = 1$  cps) in agreement with structure 14.

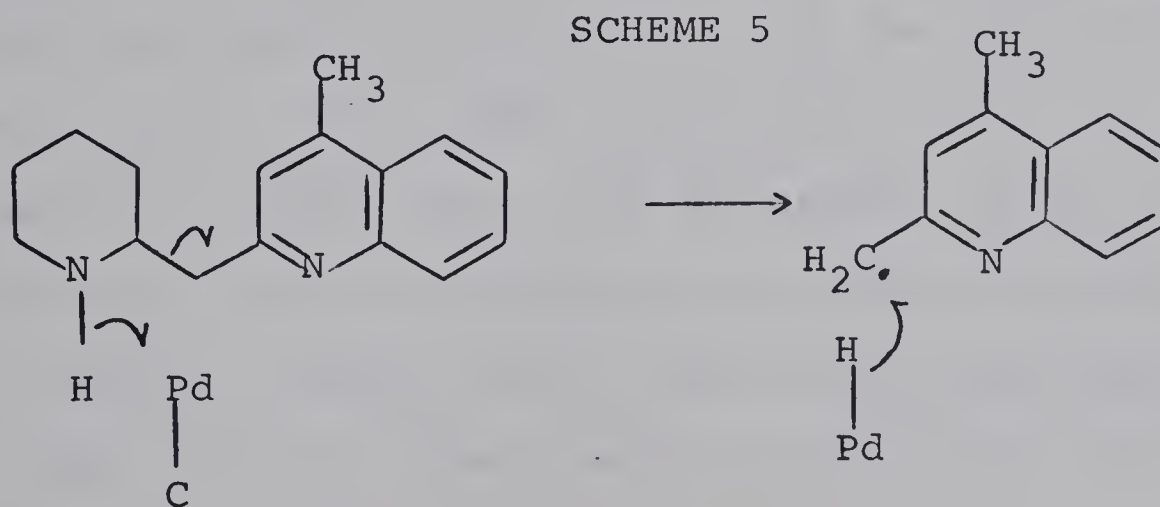


14

As mentioned above, the mass spectra of both the olefin 13 and the dihydro compound 14 indicated that they had the expected molecular weights. However due to the fact that the parent peaks in the olefin and especially in the dihydro compound were weak in intensity, a portion of the dihydro compound was acetylated. The acetylated material was chromatographed on alumina and distilled. The product was shown, according to its behavior on thin layer alumina plates, to be pure and according to its mass spectrum to have a molecular ion at  $m/e$  282 (19) as expected. The infrared spectrum showed strong, broad absorption at  $1640\text{cm}^{-1}$ , typical of a tertiary amide, while the nmr indicated what appeared to be two N-acetyl signals at  $\tau$  8.06 and  $\tau$  8.12. The appearance of two signals instead of one is perhaps due to the presence of rotomers.



Various attempts to dehydrogenate<sup>77</sup> the dihydro-olefin were carried out in tetralin at 180° using Pd/C, at 250° using the same reagents in a sealed tube, and using selenium at 305° in a sealed tube. In each case 2,4-dimethylquinoline was isolated as the major product. Attempts to dehydrogenate the olefin with Pd/C in tetralin and with selenium also yielded 2,4-dimethylquinoline. Presumably the mechanism for the formation of the quinoline involves dehydrogenation-hydrogenation steps with transfer of hydrogen to and from the catalyst as shown for Pd in Scheme 5.



Dehydrogenation using 2,3-dichloro-5,6-dicyano-p-benzoquinone<sup>78</sup> and 9,10-phenanthraquinone were also attempted. Both reactions gave back starting material.

By considering the two dehydrogenation products 2-n-pentyl- and 2-n-hexyl-4-methyl-6-n-butylpyridine, it was possible to arrive at a reasonable working

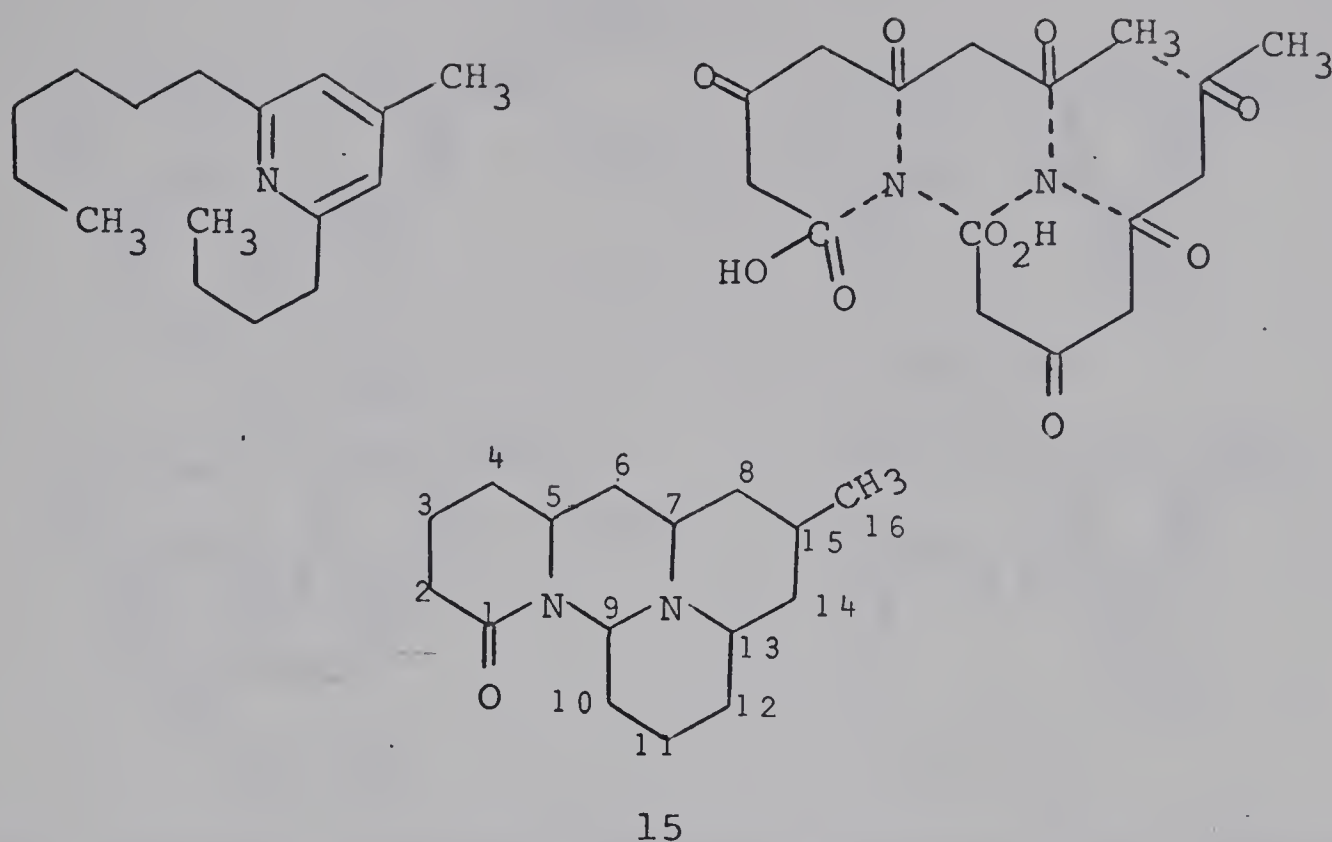


hypothesis for the structure of cernuine. This hypothesis assumes that the dehydrogenation products arise without rearrangement of the carbon skeleton. It should first be pointed out that Conroy<sup>79</sup> has proposed a plausible biogenetic scheme for the Lycopodium alkaloids involving the condensation of two 3,5,7-triketooctanoic acid equivalents. Assuming that the C<sub>16</sub> dehydrogenation product arises from cernuine (C<sub>16</sub>) without rearrangement that has been biosynthesized from two of these chains, and that the C-methyl of the pyridines represents the C-methyl group of cernuine, and that this group is derived from the terminal methyl of one of the polyoctanoic acid chains, then aldol condensation of the C-7 carbonyl of this chain with the methyl groups of the other chain and condensation with two equivalents of ammonia (dashed lines) followed by adjustment of the oxidation level leads to structure 15 for cernuine.

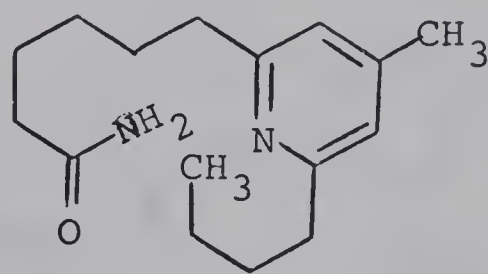
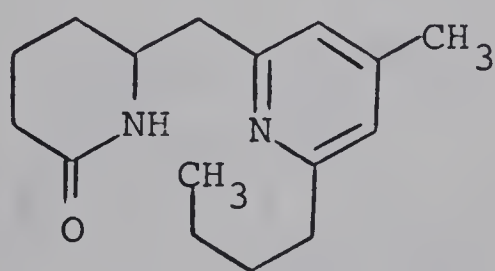
In Scheme 6 is depicted the C<sub>16</sub> pyridine, the condensation involving the two ketooctanoic acid units, and the proposed structure for cernuine.



## SCHEME 6



The formation of the two amide-pyridine dehydrogenation products 5 and 6 can also be rationalized on the basis of the structure proposed for cernuine. Their structures can now be tentatively written as 16 and 17

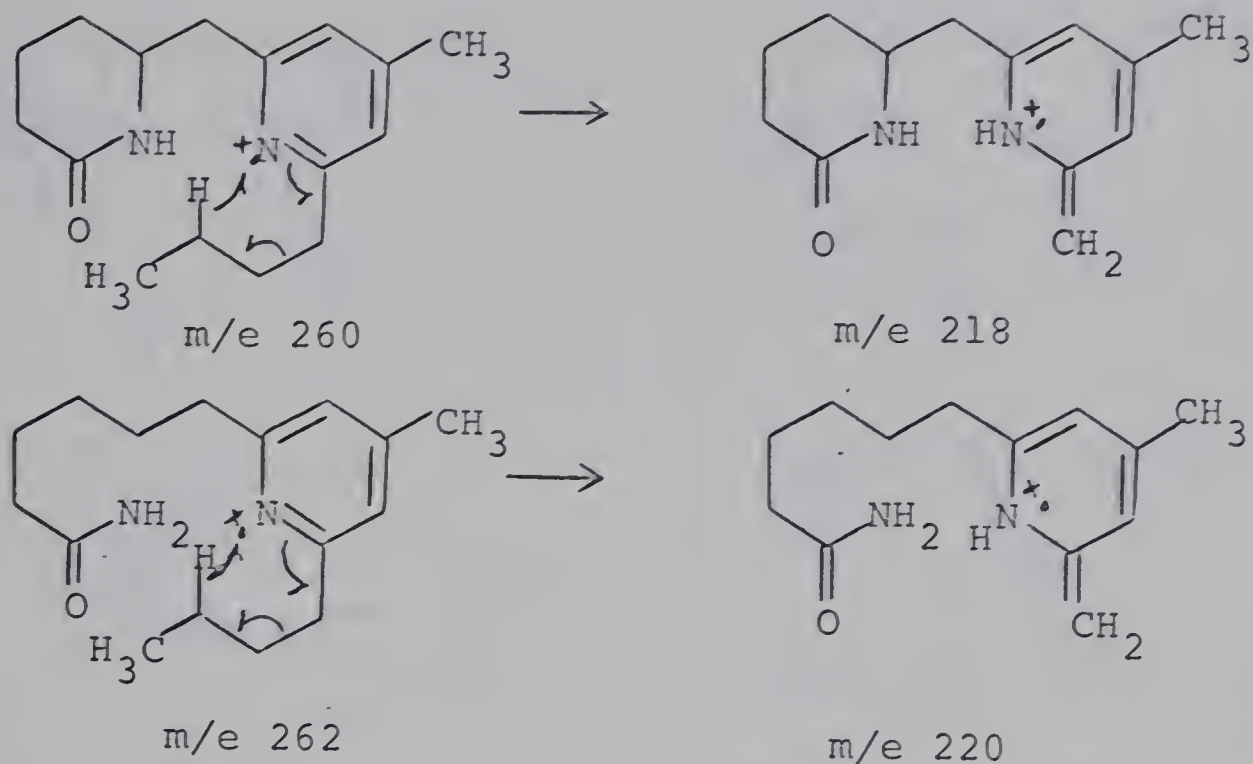


16  
17  
Both dehydrogenation products show intense  $M^{+}-42$  peaks at  $m/e$  218 (34) and  $m/e$  220 (40). These peaks may be explained by the loss of a propene unit in a McLafferty rearrangement<sup>80a</sup> as shown in Scheme 7.



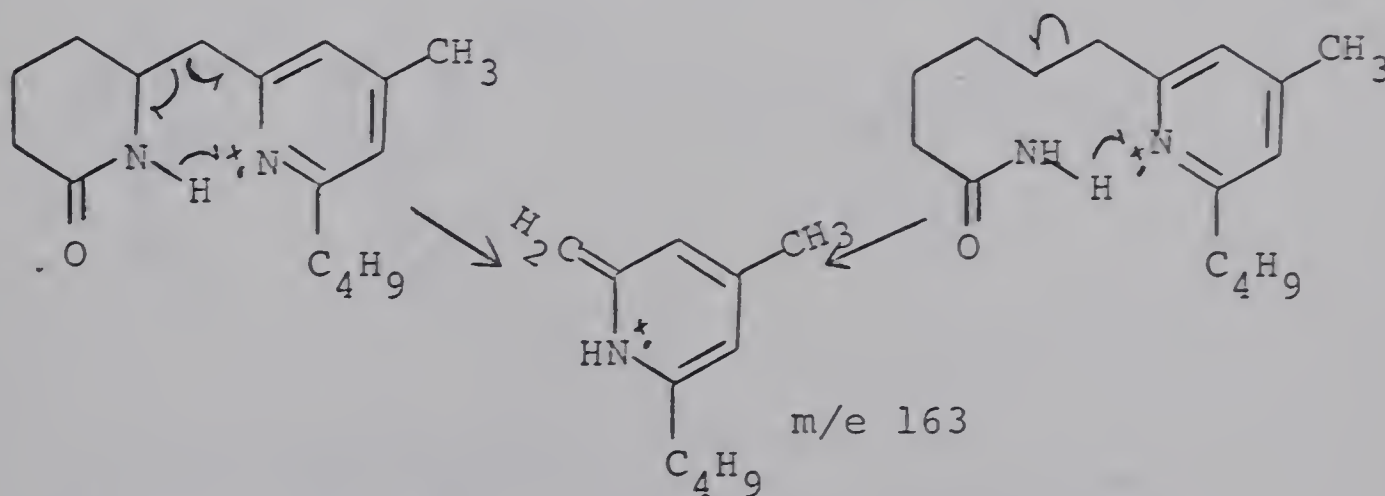


SCHEME 7



In each mass spectrum, the base peak is at  $m/e$  163(100). This can be explained on the basis of a simple H radical abstraction and  $\beta$ -cleavage as shown in Scheme 8.

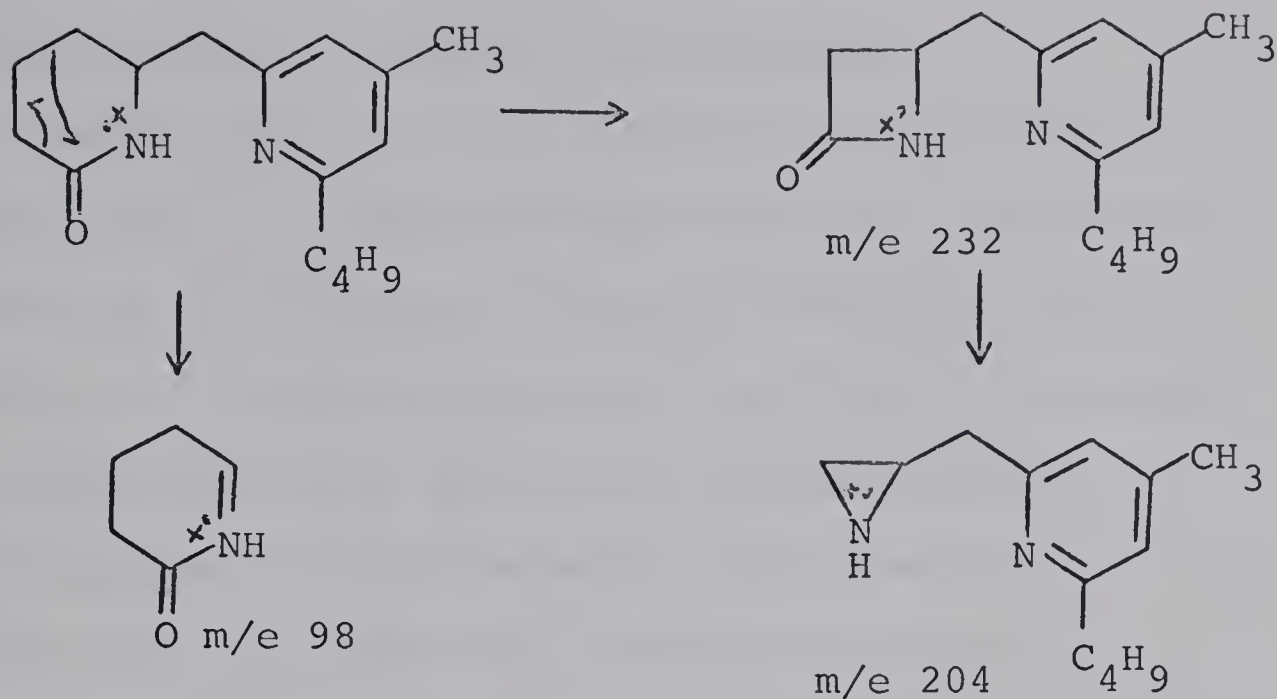
SCHEME 8



For dehydrogenation product 16, minor peaks were observed at  $m/e$  232(4), 204(3) and 98(21) which could arise in the following manner<sup>80b</sup> as shown in Scheme 9.

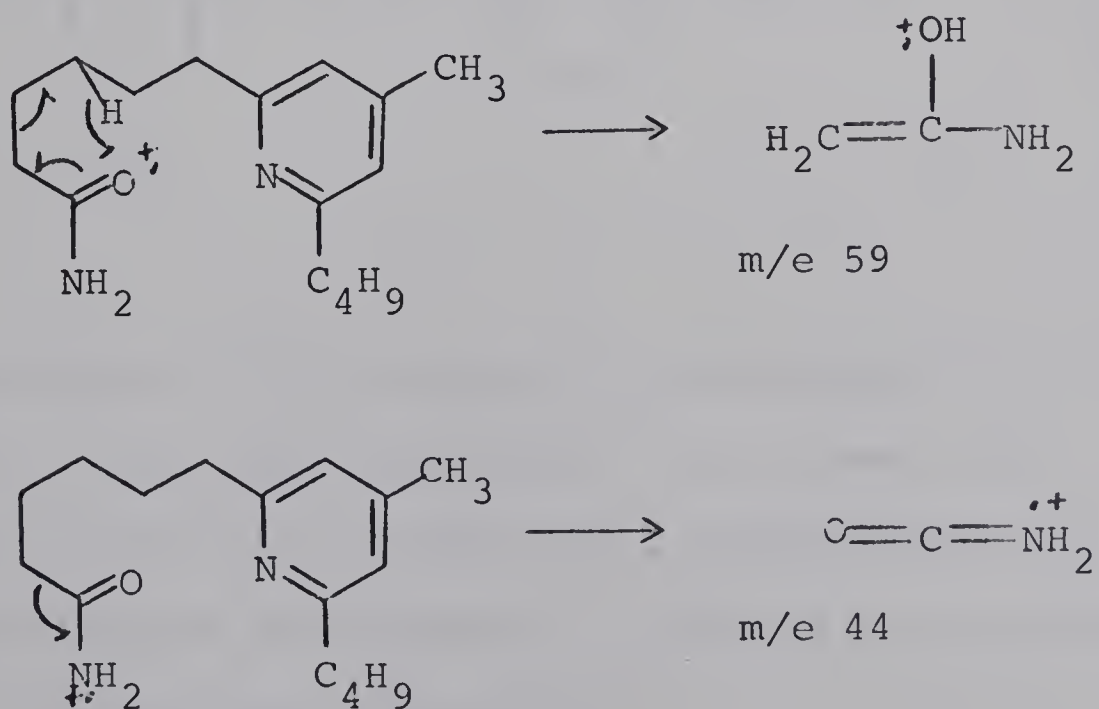


SCHEME 9



For dehydrogenation product 17 minor peaks were observed at  $m/e$  59(3) and  $m/e$  44(10) which might correspond to the following cleavages<sup>80c</sup>.

SCHEME 10

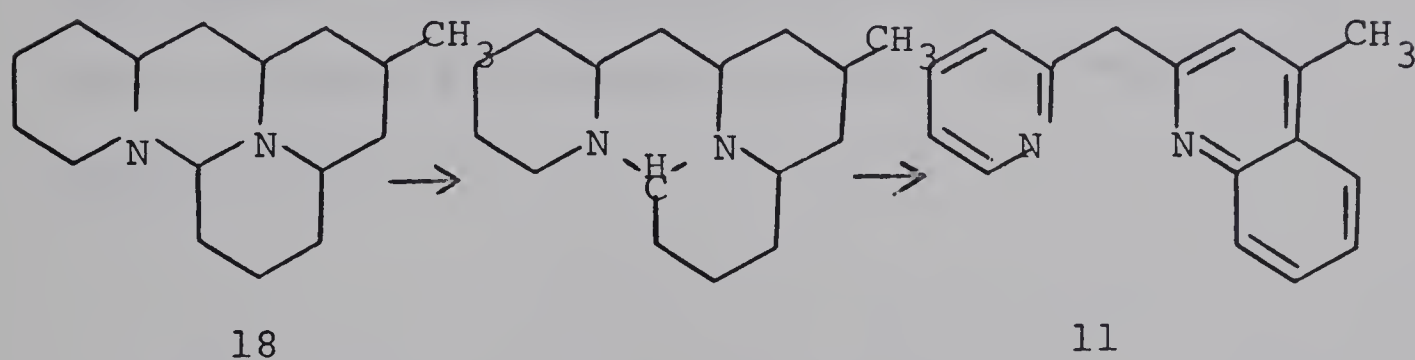




No further evidence for the structures of these dehydrogenation products was obtained.

On the basis of the structure 18 for dihydrodeoxycernuine, which follows from that proposed for cernuine, the pyridine-quinoline dehydrogenation product 11, tentatively identified as 2-[ $\alpha$ -picoly1]-4-methylquinoline must arise by some cleavage-rearrangement-dehydrogenation (not necessarily in that order) pathway such as outlined below in Scheme 11.

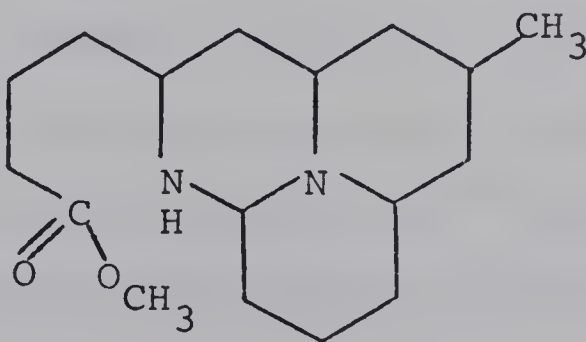
SCHEME 11



A precedent for this type of rearrangement may be found in the work of Prelog<sup>63</sup>, who showed that quinolizidine when subjected to dehydrogenating conditions in the presence of palladium on carbon or selenium gives quinoline.



Cernuine was recovered unchanged from attempted hydrogenolysis using  $\text{PtO}_2$  in either neutral or acidic methanol, and from attempted hydrolyses using 15% KOH in ethanol and in methyl cellosolve (2-methoxyethanol). However, 15% KOH in ethylene glycol at  $190^\circ$  brought about hydrolysis. Esterification of the hydrolysis products with diazomethane followed by chromatography on alumina yielded a product which showed in its infrared spectrum ( $\text{CCl}_4$ ) a sharp peak at  $1730\text{ cm}^{-1}$ , typical of an ester carbonyl. No NH or OH absorption was observed. The mass spectrum of this substance indicated a molecular ion at  $m/e\ 294(50)$ . The substance was not further identified, although the molecular weight corresponds to structure 19.



19





Oxidation of cernuine using potassium permanganate yielded starting material (60%) and product (40%). Esterification of the product with diazomethane followed by chromatography on alumina gave a poor yield of material which could not be characterized.

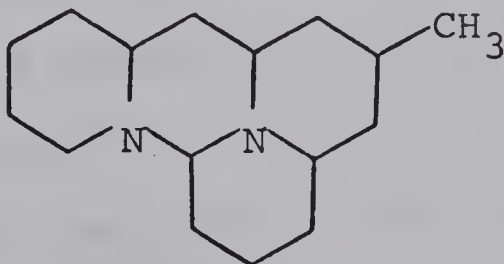
Attempted Hofmann degradation of cernuine methiodide, carried out by refluxing the methiodide in tertiary-butyl alcohol containing potassium tertiary-butoxide, yielded a mixture of four components, the major one being cernuine. Likewise, attempted Hofmann degradation on cernuine methoxide (prepared by passing the methiodide through an ion exchange column,  $\text{OH}^-$  form) yielded only cernuine as shown by an infrared spectral comparison.

Hydrogenation of the methiodide using  $\text{PtO}_2$  in methanol yielded a colorless crystalline substance. The infrared spectrum (Nujol) showed weak absorption at 3510 and 3490  $\text{cm}^{-1}$  indicating an NH function, strong absorption at 1635  $\text{cm}^{-1}$  typical of a secondary lactam carbonyl and a complex fingerprint region not identical with that of cernuine. No further characterization was done on this material.



Lithium aluminum hydride reduction of cernuine methiodide yielded dihydrodeoxycernuine, identified by thin layer chromatography, as well as three other products more polar than the methiodide. One of the three products was shown to be identical (by tlc comparison) with the  $\text{NaBH}_4$  cleavage product of dihydrodeoxycernuine monomethiodide (to be discussed later).

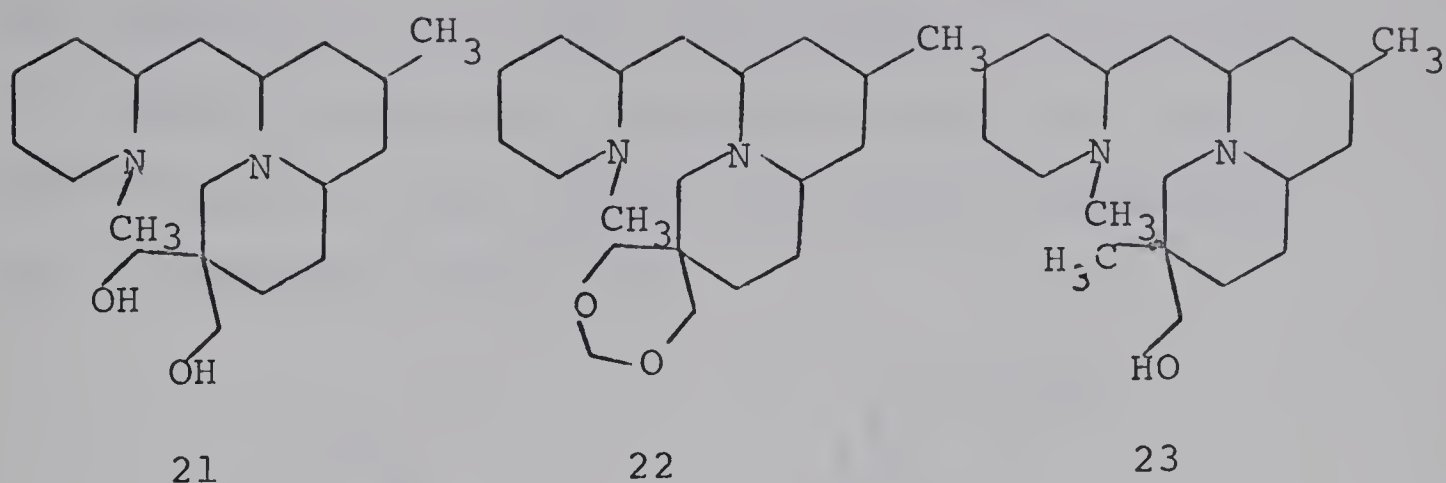
A more informative degradation was realized utilizing the lithium aluminum hydride reduction product of cernuine, dihydrodeoxycernuine (18).



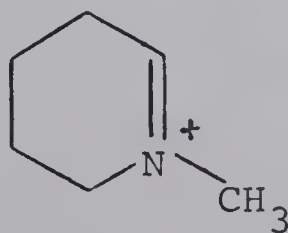
18

Treatment of dihydrodeoxycernuine with a 1:1 mixture of 98% formic acid - 40% formaldehyde yielded three products, 21, 22 and 23, the structures of which could be interpreted on the basis of the structure proposed for dihydrodeoxycernuine.





The infrared spectrum ( $\text{CCl}_4$ ) of 21 showed absorption at 3620 and 3300  $\text{cm}^{-1}$  (broad), the latter of which was shown by a dilution study to be due to intramolecular hydrogen bonding. The nmr spectrum showed a broad two proton multiplet at  $\tau 5.35$ , perhaps due to the OH protons, two two-proton  $\text{O}-\text{CH}_2-$  singlets at  $\tau 6.35$  and 6.50, a three proton  $\text{N}-\text{CH}_3$  singlet at  $\tau 7.58$ , and a three proton secondary methyl doublet at  $\tau 9.01$ . The mass spectrum of this material did not show a molecular ion at  $m/e$  324, however it did show an intense peak at  $m/e$  98(90) which is attributed to fragment 24.

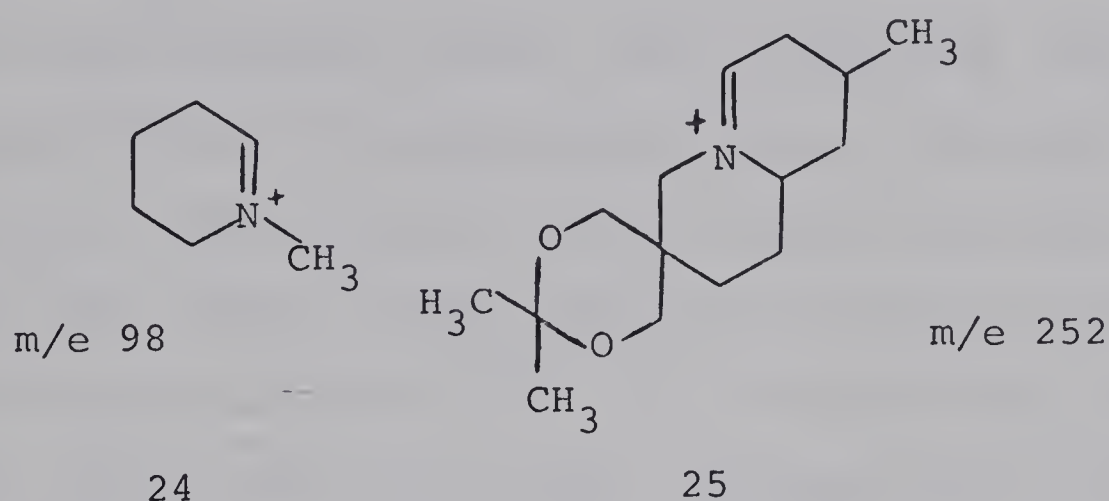


$m/e$  98

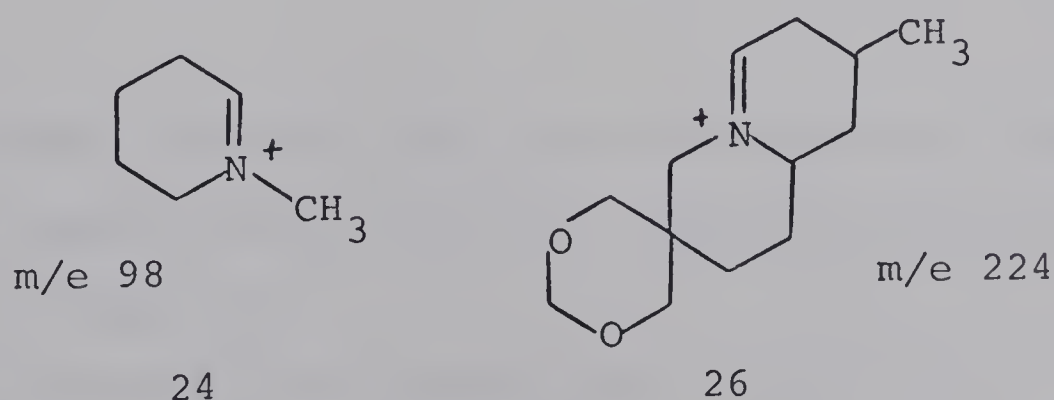
24



The acetonide of the diol was prepared <sup>86</sup> and showed the expected molecular ion at  $m/e$  364(6) with two intense peaks at  $m/e$  252(43) and 98(100) presumably due to fragments 24 and 25.



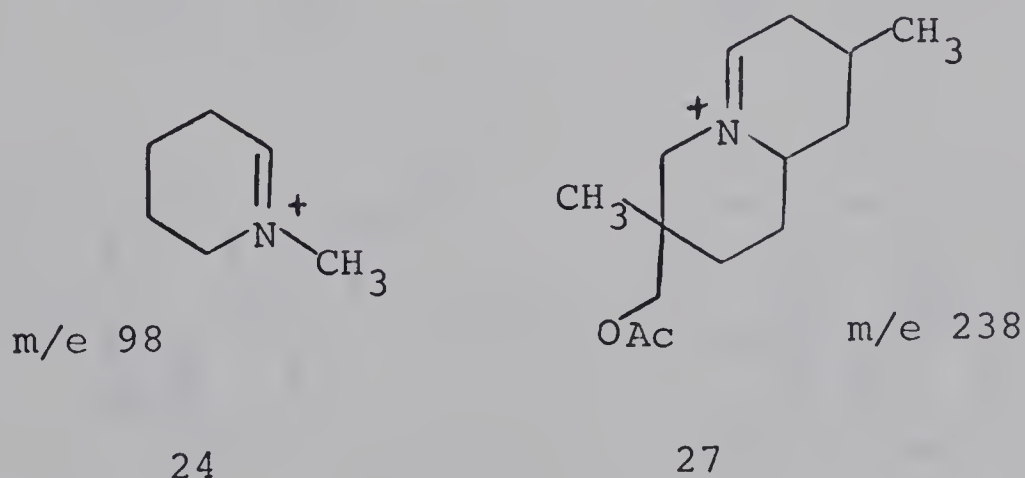
Product 22 did not show OH absorption in the infrared. Upon acetylation the material was recovered unchanged. The mass spectrum showed a molecular ion at  $m/e$  336(7) with intense peaks at  $m/e$  224(53) and 98(100). These peaks can be assigned to the two fragments 24 and 26.







The nmr spectrum of product 23 displayed a one proton multiplet at  $\tau$ 4.43 (OH?), a two proton doublet at  $\tau$ 6.42, a three proton singlet at  $\tau$ 7.58 attributable to the N-CH<sub>3</sub>, a three proton doublet at  $\tau$ 8.99 (J=6 cps) due to the secondary methyl, and a singlet at  $\tau$ 9.17 arising from the tertiary methyl group. The mass spectrum of this material did not show a molecular ion at m/e 308, however after acetylation the mass spectrum showed a parent peak at m/e 350(5) with intense peaks at m/e 238(68) and m/e 98(100) corresponding to the fragments 24 and 27.



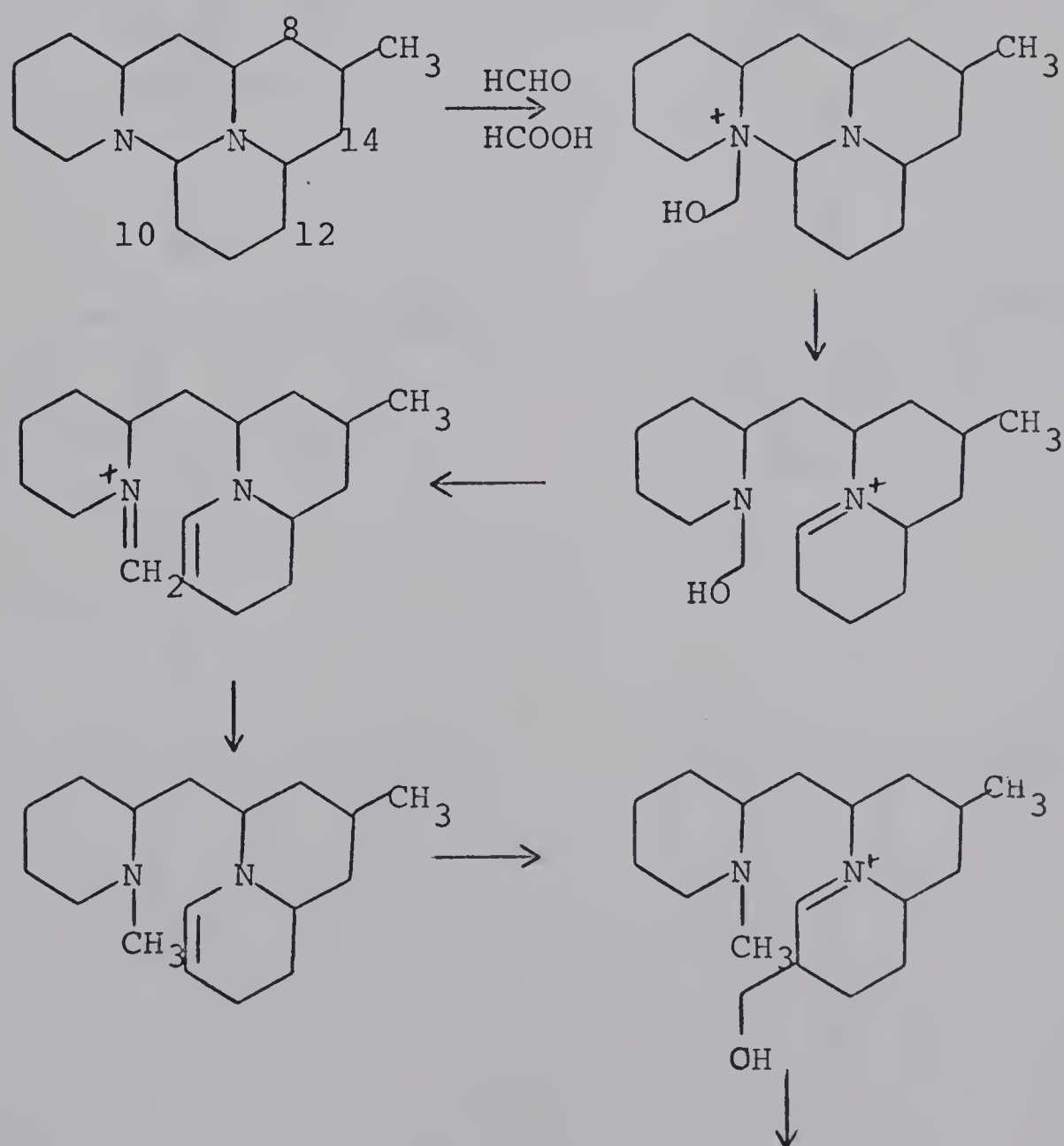
An infrared spectrum (CCl<sub>4</sub>) on the acetylated material showed absorption at 1720 cm<sup>-1</sup> indicative of the O-acetyl function.

The formation of products 21, 22 and 23 is explained in Scheme 12 on the basis of the proposed structure 18 for dihydrodeoxycernuine. The mass spectra of the products and/or derivatives indicate



that initial cleavage during the reaction must have taken place between the nitrogens in the manner shown. No evidence has been presented that the attack of formaldehyde did take place on C-10. By equilibration of the immonium form of the enamine to other isomeric enamines, attack of formaldehyde might possibly have taken place at C-12, C-14 or C-8.

SCHEME 12

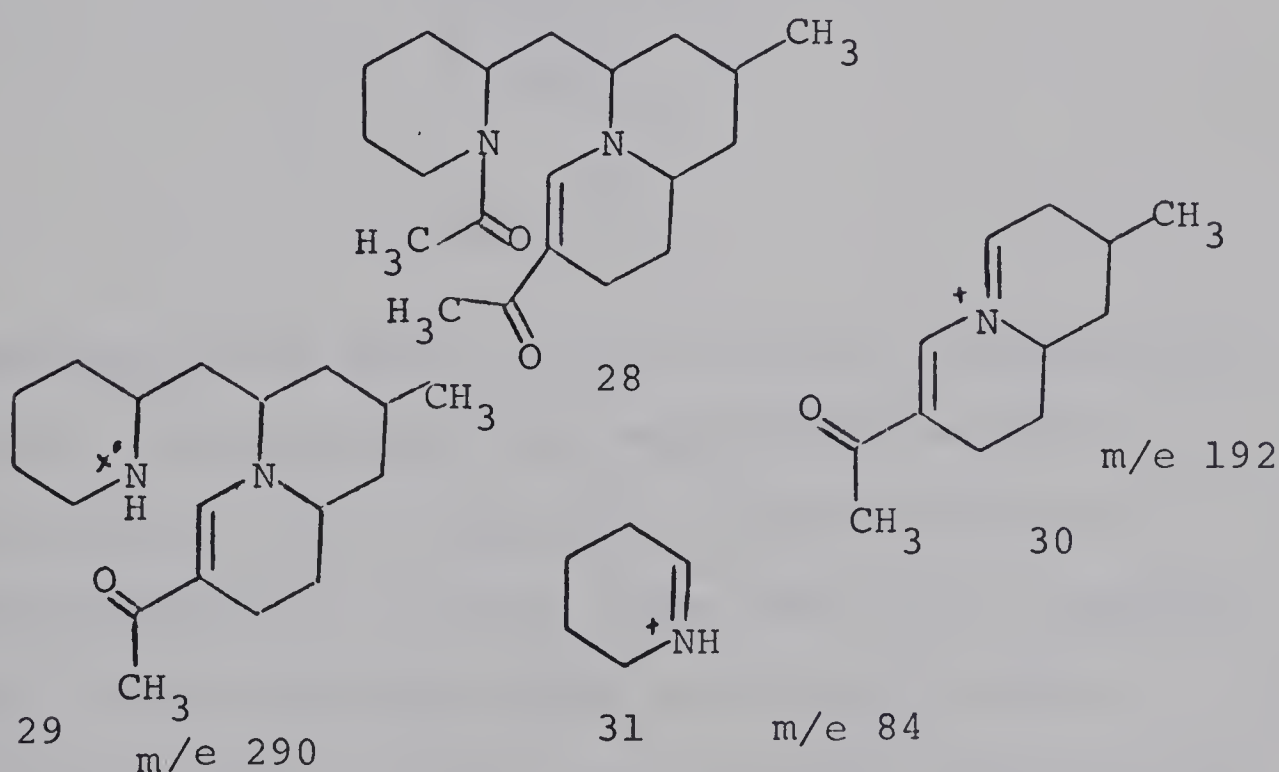








When dihydrodeoxycernuine was heated in acetic anhydride it yielded after purification a small amount of material that showed absorption at  $1625\text{ cm}^{-1}$  in the infrared ( $\text{CCl}_4$ ) and a maximum at  $312\text{ m}\mu$  in the ultraviolet. A mass spectrum of the substance showed a molecular ion at  $m/e$  332(14) with major peaks at 290(100), 192(35) and 84(27). The most reasonable structure based upon this data is 28, with possible structures 29, 30 and 31 for the fragments observed.



Attempted cleavage of dihydrodeoxycernuine with 98% formic acid yielded only starting material.

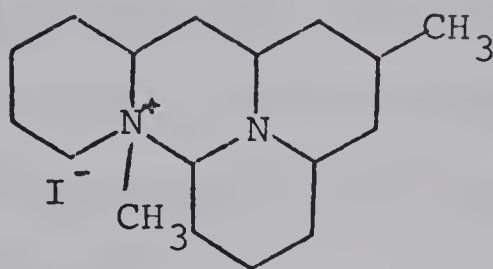
Attempted hydrogenolysis of dihydrodeoxycernuine with  $\text{Pd/C}$  in methanol ( $\text{H}^+$ ) and with  $\text{Rh/Al}_2\text{O}_3$ ,  $\text{Rh/Al}_2\text{O}_3$  and  $\text{PtO}_2$ , and  $\text{Pd/C}$  in glacial acetic acid





all resulted in recovery of starting material.

Cleavage of the N-C-N bond in the monomethiodide of dihydrodeoxycernuine proceeds, as deduced by mass spectrometry, in a manner analogous to that which took place in the formaldehyde-formic acid and acetic anhydride cleavage reactions. Dihydrodeoxycernuine monomethiodide (30), mp 236-238°, was prepared by



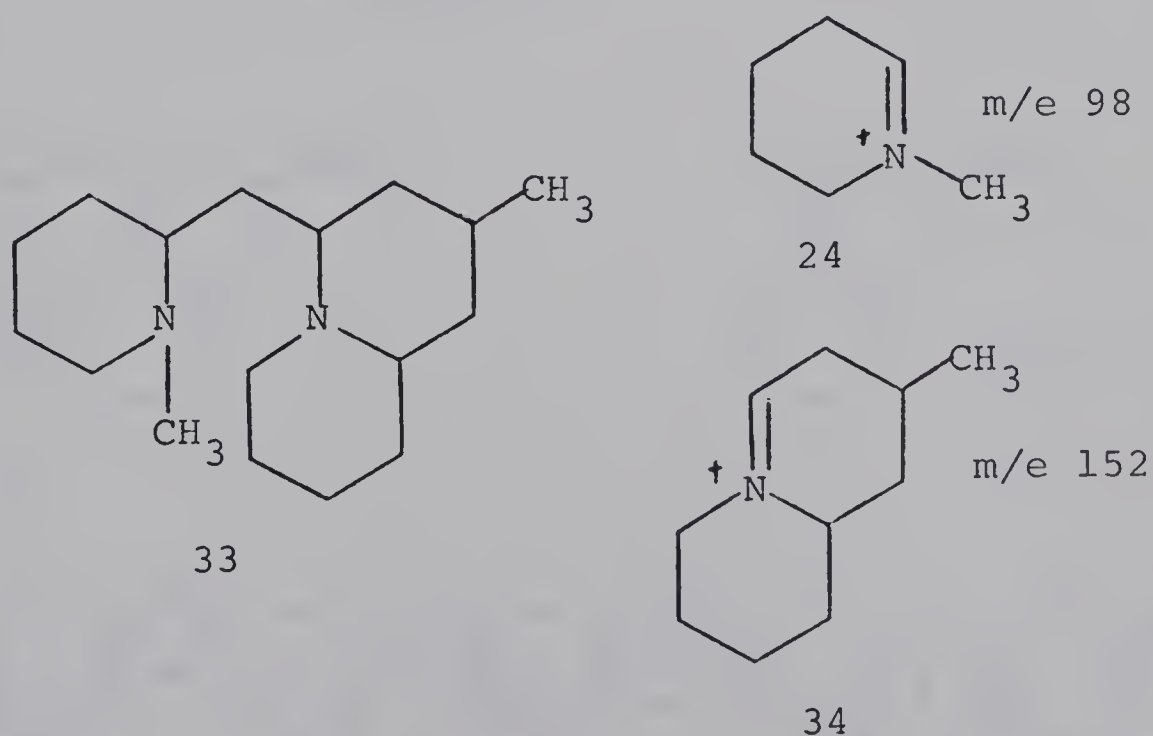
32

treatment with methyl iodide at room temperature in ether. The fact that the methiodide was not a mixture of the two possible monomethiodides was demonstrated by its thin layer behavior on alumina and its nmr spectrum which exhibited a single  $\begin{array}{c} +\text{I} \\ | \\ -\text{N}-\text{CH}_3 \\ | \end{array}$  peak at  $\tau 6.44$ . The analysis, although not particularly good, was in better agreement with a monomethiodide than a dimethiodide.

Attempted formation of salts with ethyl iodide, isopropyl iodide and 1,3- dibromopropane was unsuccessful.



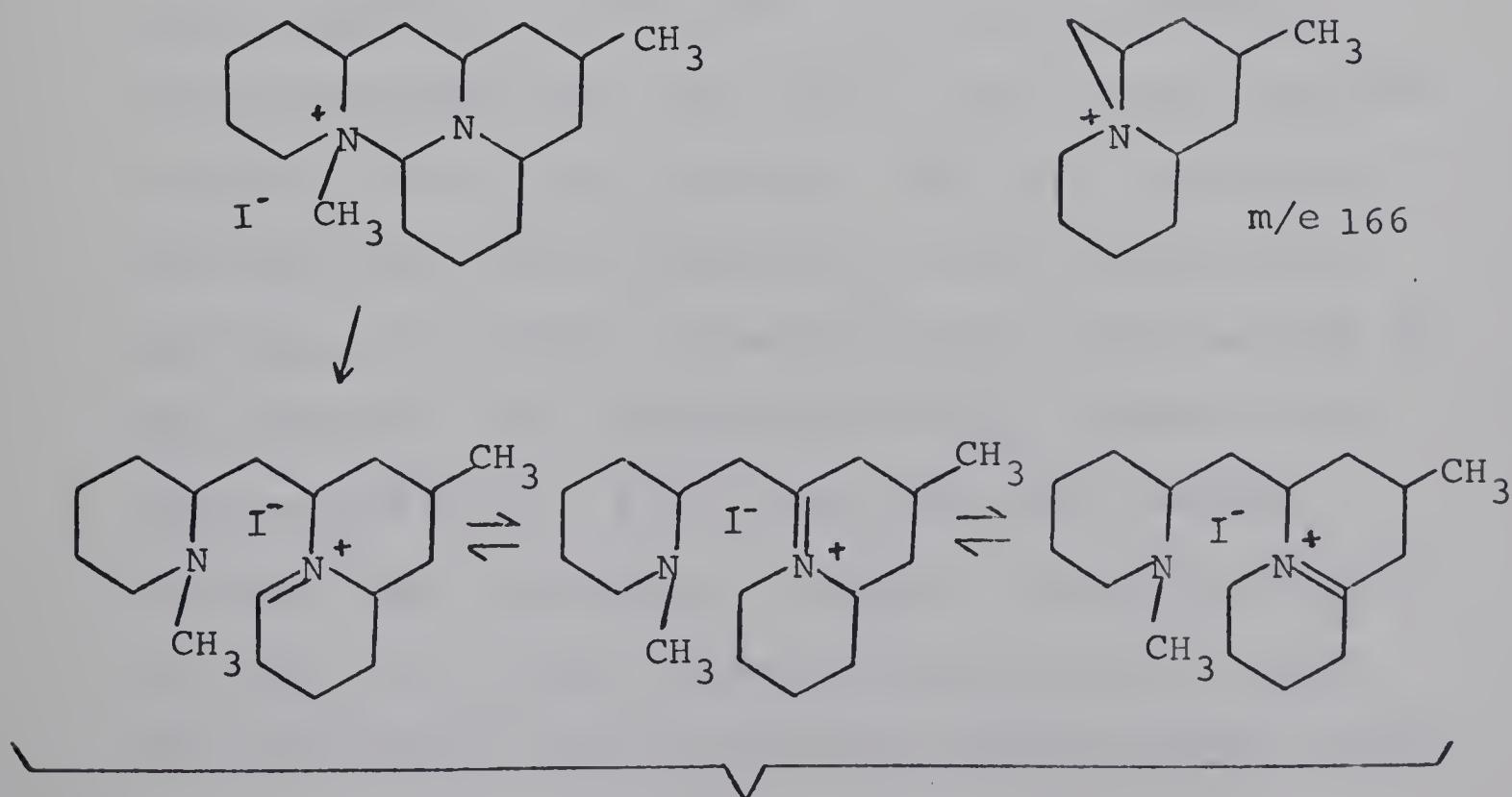
The cleavage of the monomethiodide of dihydrodeoxycernuine was carried out using  $\text{NaBH}_4$  in refluxing ethanol. The crude reaction product contained mainly, according to thin layer behavior, starting material and a less polar product. The crude product was purified first by column chromatography then by ptlc on alumina. The major product showed in its mass spectrum a molecular ion at  $m/e$  264(11) with intense peaks at  $m/e$  152(100) and 98(71). The formation of fragments 24 and 34 is feasible if the monomethiodide has structure 32 and the cleavage product has structure 33.





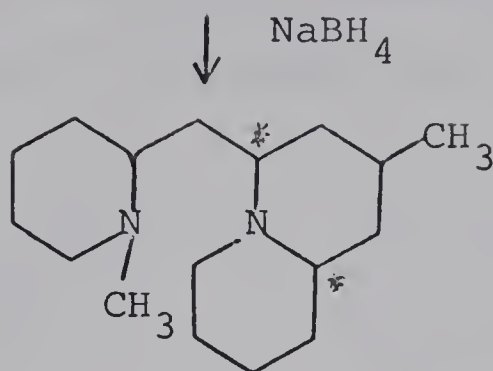
The nmr spectrum of the cleavage product indicated a singlet at  $\tau$ 7.80, typical of an N-CH<sub>3</sub> group. A more polar minor product which was isolated also showed a molecular ion at m/e 264(14), however, besides a major fragment at m/e 98(55) one was observed this time at m/e 166(100) with a less intense fragment at m/e 152(28). The minor product is possibly an epimer of 33 (at C-7 or C-13). Scheme 13 gives a possible fragment corresponding to m/e 166 and a possible mode of formation of the epimer.

SCHEME 13





## SCHEME 13 (cont.)



33

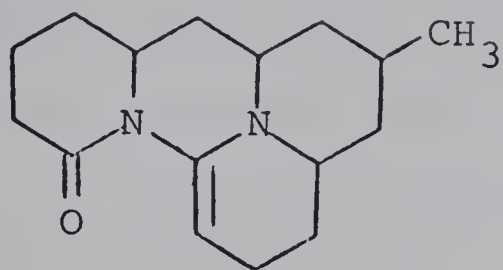
Hydrogenolysis of the dihydrodeoxycernuine monomethiodide with Pd/C in methanol yielded a product identical with the major product from the NaBH<sub>4</sub> reduction. The results described to this point support the structure assigned to cernuine.

Some insight into the stereochemistry of cernuine was gained by a study of the mercuric acetate oxidation of cernuine. The oxidation product, obtained in 70% yield, was characterized as its perchlorate salt, mp 174.5 - 175°, which analyzed correctly for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O·HClO<sub>4</sub>. The mass spectrum on the free base also indicated that one unsaturation had been introduced. A molecular ion was observed at m/e 260(35). The nmr spectrum (CCl<sub>4</sub>) showed a one proton doublet at τ4.35 (J=10 cps) which showed further small splitting, a complex two proton signal at τ5.8 - 6.0, and a three proton doublet at τ9.08. The possibility existed that the product might correspond to any one of the five enamines 35, 36, 37, 38

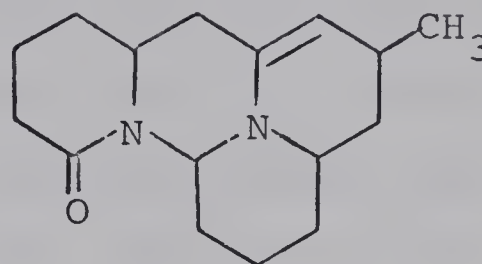




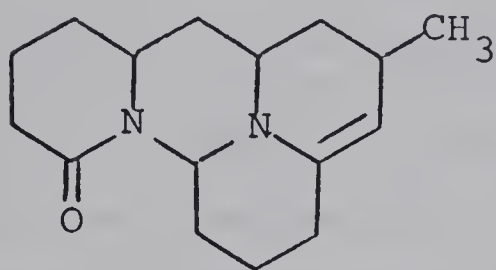
and 39, however nmr data and a comparison with anhydrolycocernuine\* 38 excluded all but structure 39.



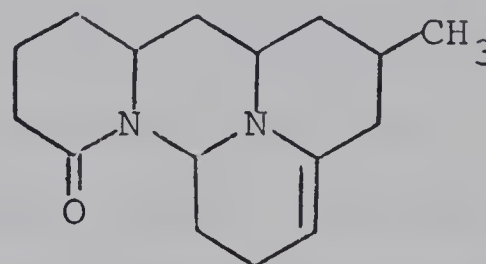
35



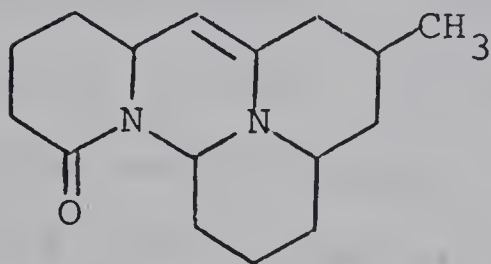
36



37



38



39

Structure 35 as a possibility is ruled out by the fact that the C-9 proton, observed in cernuine at  $\tau$ 4.53, is still present, now at  $\tau$ 4.38. Structures 36 and 37 can be excluded because the methine proton

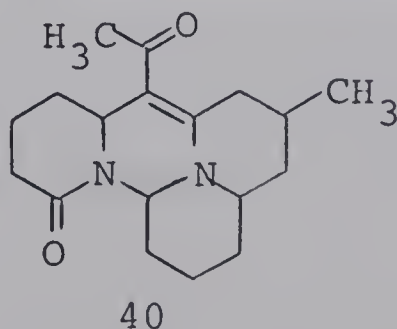
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\*Work carried out by S. Valverde-Lopez in this laboratory.



on C-15 at approximately  $\tau 8.1$ , as shown by spin decoupling, was at the same position as in cernuine, and therefore not allylic. Structure 38 is the known anhydrolycocernuine, and since this was shown by its infrared spectrum and tlc behavior not to be identical with the mercuric acetate oxidation product, the latter must be the  $\Delta^{6,7}$  isomer 39. The ultraviolet spectrum of the enamine showed a maximum at 217  $m\mu$ . Acetylation of the enamine with acetic anhydride-pyridine yielded a product 40 whose nmr spectrum confirmed again the presence of a  $\Delta^{6,7}$  double bond. The mass spectrum of the product showed the expected molecular ion at  $m/e$  302(52). The ultraviolet showed a maximum at 325  $m\mu$  ( $\epsilon$ 1200). The nmr spectrum of 40 revealed that the methine proton at C-15 still absorbed at  $\tau 8.1$ , the C-9 proton appeared as a doublet, further split, at  $\tau 4.36$ , the C-5 proton was a quartet at  $\tau 5.45$  ( $J=10$  cps and 3 cps), the acetyl methyl appeared as a singlet at  $\tau 7.84$  and the C-15 methyl as a doublet at  $\tau 9.05$ .

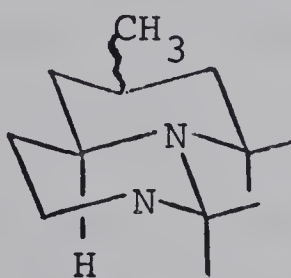
Hydrogenation of the acetylated enamine yielded a product that showed in its mass spectrum a molecular ion at  $m/e$  304(10).





Mercuric acetate oxidation has been shown to proceed preferentially toward the  $\alpha$  carbon which possesses a hydrogen that has a trans-diaxial relationship to the lone pair on the nitrogen<sup>82</sup>.

Lycocernuine\* as well as cernuine undergo mercuric acetate oxidation toward C-7, thus it is likely that the hydrogen at C-7 in cernuine is trans-diaxial to the lone pair on the nitrogen. We can thus write the following stereochemical part structure 41 for cernuine.



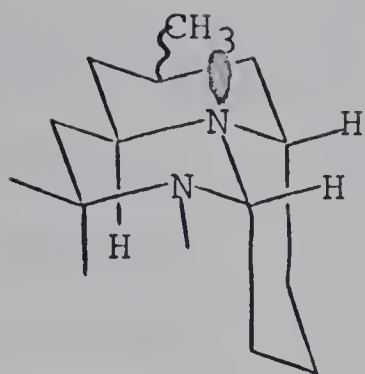
41

Bohlmann<sup>83</sup> has pointed out that bands are observed in the infrared spectrum between 2700-2800  $\text{cm}^{-1}$  when there are present two or more hydrogens trans-diaxial to the nitrogen lone pair. No "Bohlmann bands" are observed for cernuine, thus the third ring of cernuine can be represented in the part stereochemical structure as 42 and not 43.

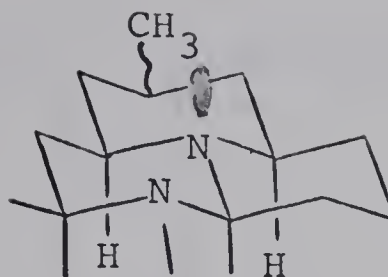
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\* S. Valverde-Lopez, Ph.D. Thesis, U. of A., 1966.





42



43

Additional information about the stereochemistry of cernuine is potentially available from studying the hydrogenation of the enamine. If the hydrogenation of the double bond takes place in a cis-fashion from the less hindered side, then, knowing the stereochemistry of the enamine, we can predict the stereochemistry at C-7 in cernuine. However, if the hydrogenation takes place involving one or more of the equilibrium forms of the enamine (the  $\Delta^{6,7}$ ,  $\Delta^{7,8}$  or immonium form) then the stereochemistry of the enamine will not necessarily determine the product of hydrogenation. The hydrogenation was carried out in a methanol-O-d solvent. Thin layer chromatographic behavior indicated the product to be identical with cernuine, however the mass spectrum (Table 3) showed that four to five deuterium atoms had been incorporated into the hydrogenation product. A possible scheme for the incorporation of the deuterium is shown in Scheme 14.

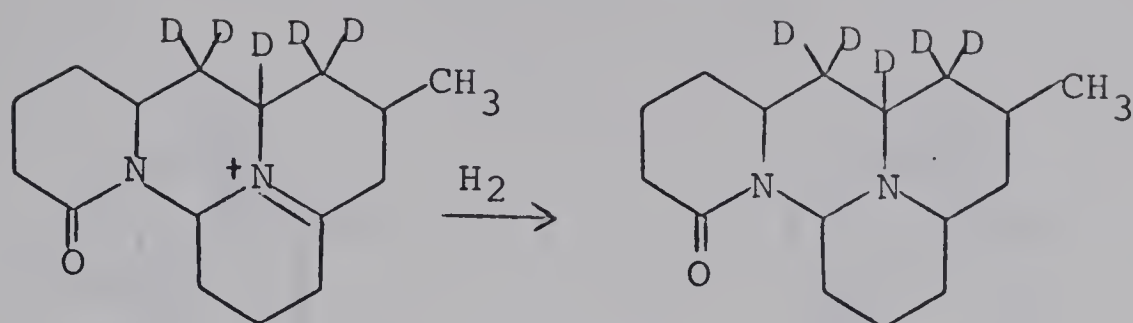








## SCHEME 14 (cont.)



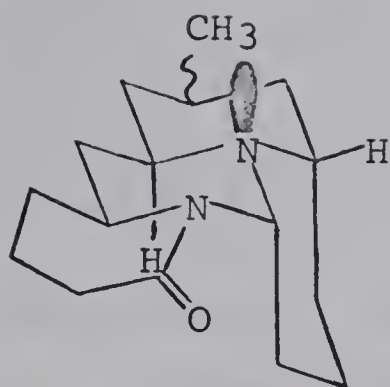
The exact location of the deuterium atoms incorporated was not investigated.

As expected, the perchlorate derivative of the enamine upon hydrogenation in methanol also gave cernuine.

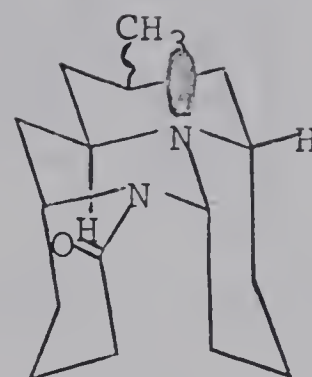
The reduction of the enamine with sodium borohydride gave cernuine with the incorporation of one atom of deuterium. The mass spectrum (Table 3) was again run under similar conditions to those for cernuine.

The stereochemistry of the fourth ring of cernuine can either be represented by formula 44 or 45. Hydride reduction of cernuine led to dihydrodeoxycernuine which showed Bohlmann bands in the infrared. The reduction products of 44 and 45 would be respectively those shown by 46 and 47. Since 46 has two hydrogens trans-diaxial to the lone pair on the nitrogen indicated and 47 has none, dihydrodeoxycernuine must be 46 and consequently cernuine, 44.

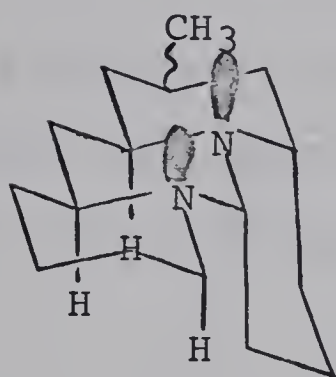




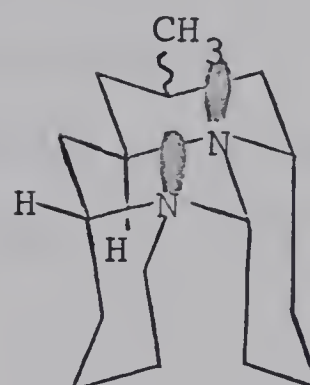
44



45



46

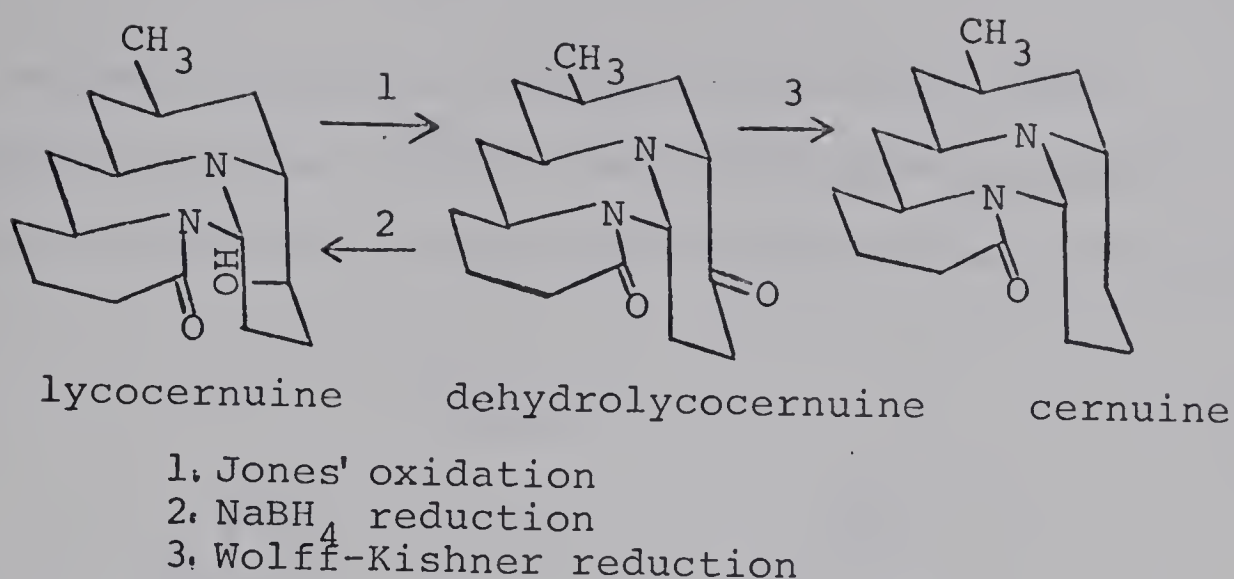


47

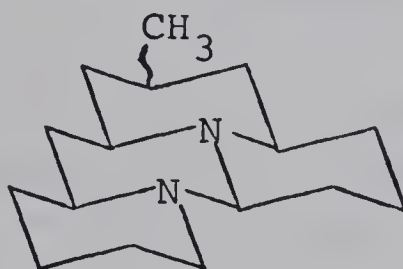
It was mentioned earlier in the discussion (p.20) that lycocernuine is hydroxycernuine. This was shown by oxidation of lycocernuine to dehydrolycocernuine then reduction to cernuine (Scheme 14A). Reduction of dehydrolycocernuine back to lycocernuine demonstrated the fact that no epimerization had taken place during oxidation. Dehydrolycocernuine was stable to base, indicating that no epimerization had taken place during the reduction to cernuine.



## SCHEME 14A



A rigorous proof of the constitution of cernuine and lycocernuine was obtained by the synthesis of dihydrodeoxyepiallocernuine (52)\*<sup>89</sup>.



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Transformation of lycocernuine into dihydrodeoxyepiallocernuine\*\*<sup>68</sup> was carried out in the following manner (see Scheme 15). Catalytic hydrogenation of anhydrolycocernuine produced allocernuine, isomeric with cernuine, which when refluxed in methanol isomerized to epiallocernuine. Reduction

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\* K.Piers, Ph.D. Thesis, U. of A., 1966.

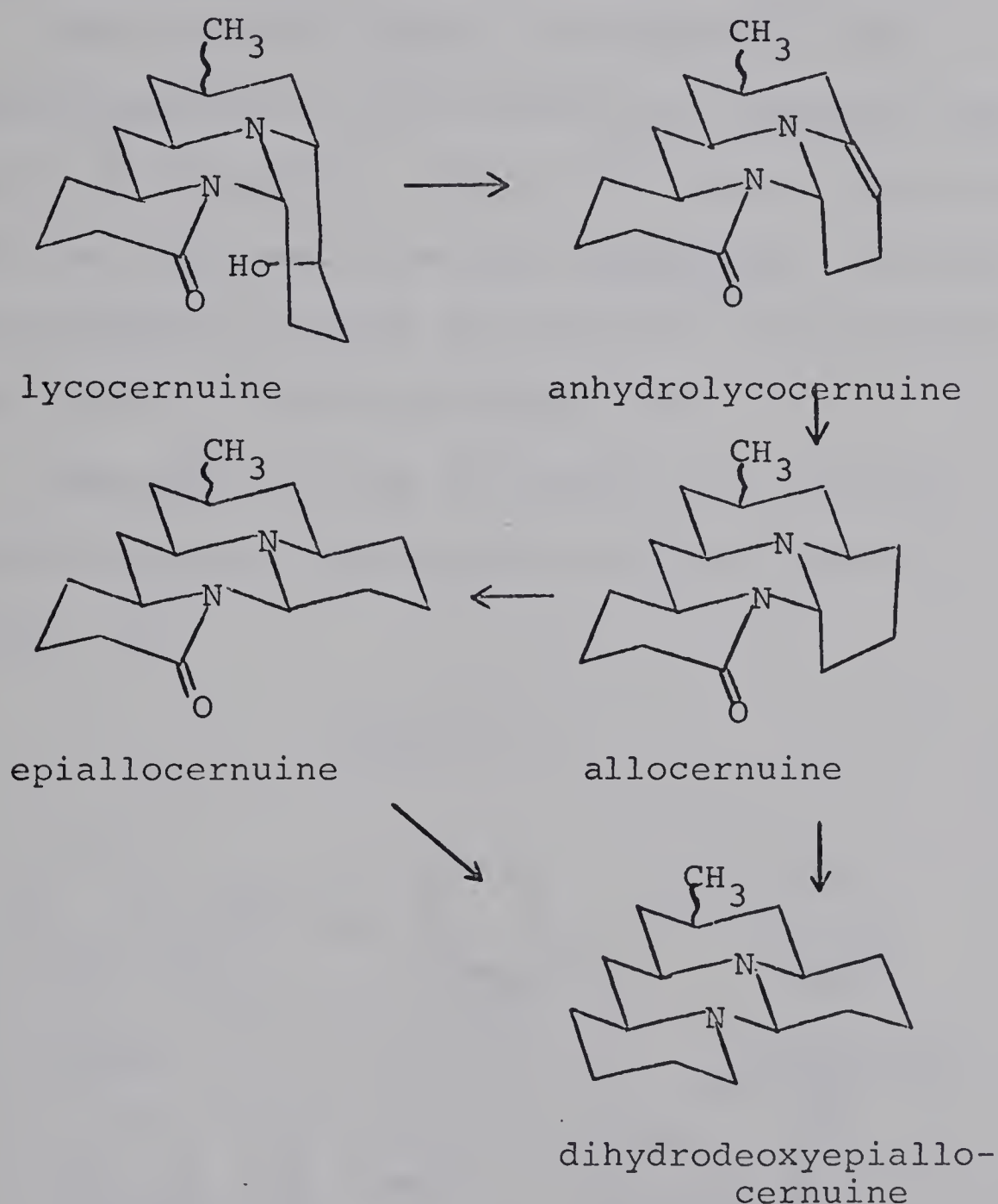
\*\* S. Valverde Lopez, Ph.D. Thesis, U. of A., 1966.





of either allocernuine or epiallocernuine with lithium aluminum hydride gave dihydrodeoxyepiallocernuine(52), the racemic form of which was synthesized\*.

SCHEME 15




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\* K. Piers, Ph.D. Thesis, U. of A., 1966.

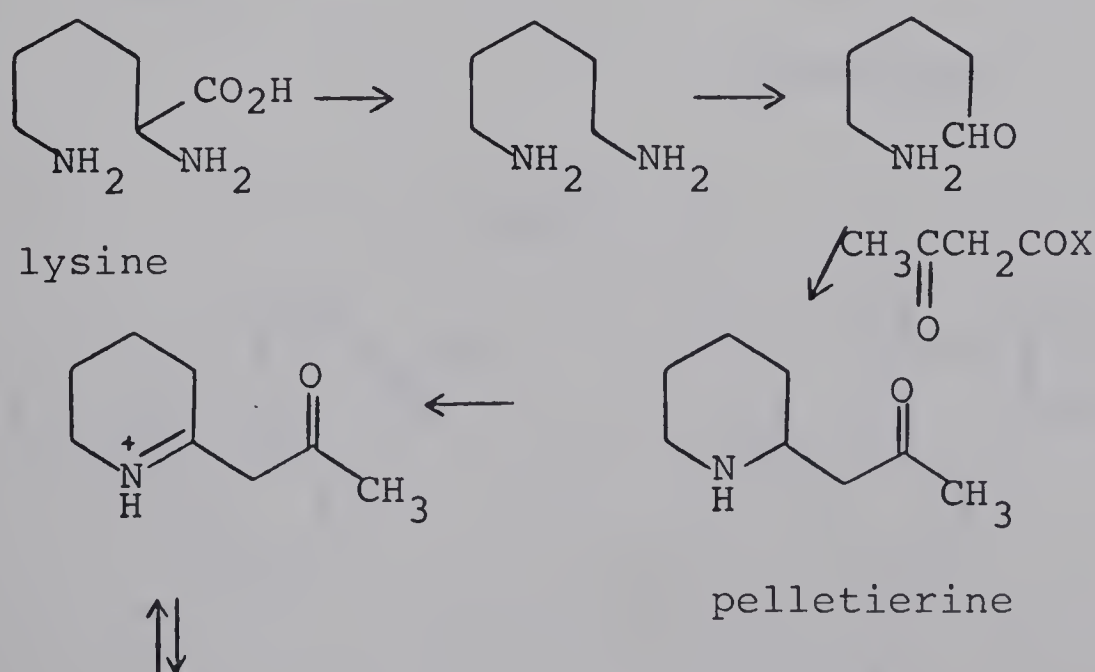


Earlier in the discussion it was shown that cernuine could be "biosynthesized" from two 3,5,7-triketo octanoic acid units, however this biogenetic scheme for the Lycopodium alkaloids lacked experimental foundation.

Very recently Spenser and MacLean<sup>94</sup> have demonstrated that lysine serves as a specific precursor of lycopodine. Their results are compatible with the hypothesis that the Lycopodium alkaloids are generated from two pelletierine units derived from lysine as shown in Scheme 15A.

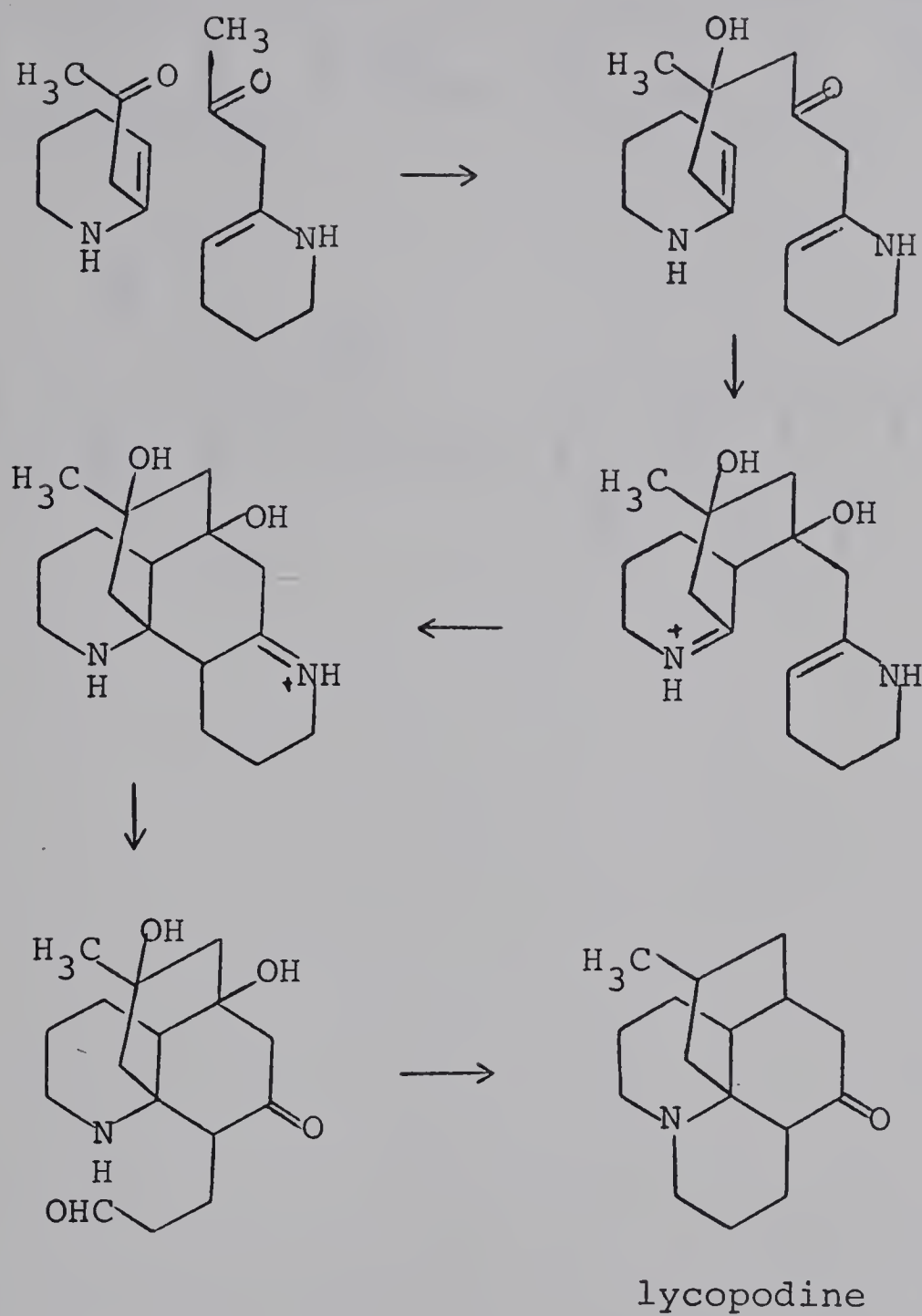
Cernuine may also be derived in a similar fashion from two pelletierine units as shown in Scheme 15B.

SCHEME 15A

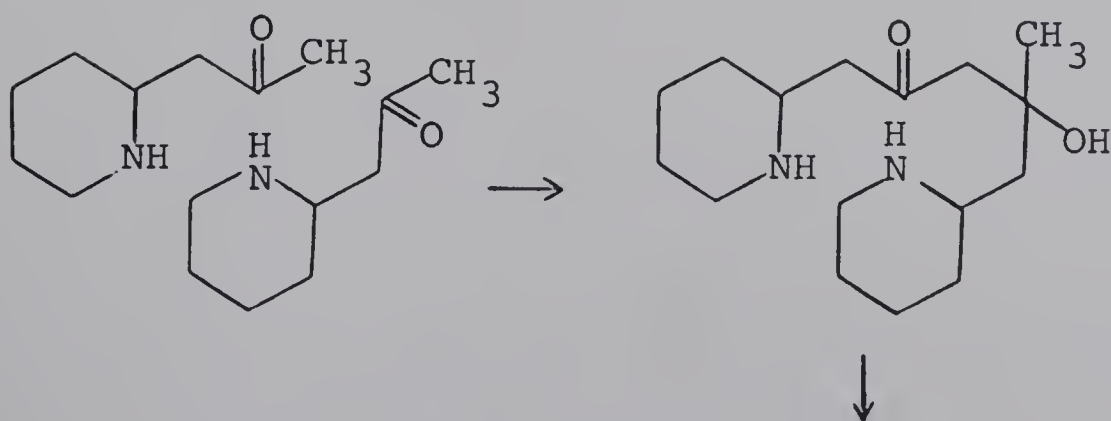




SCHEME 15A (cont.)

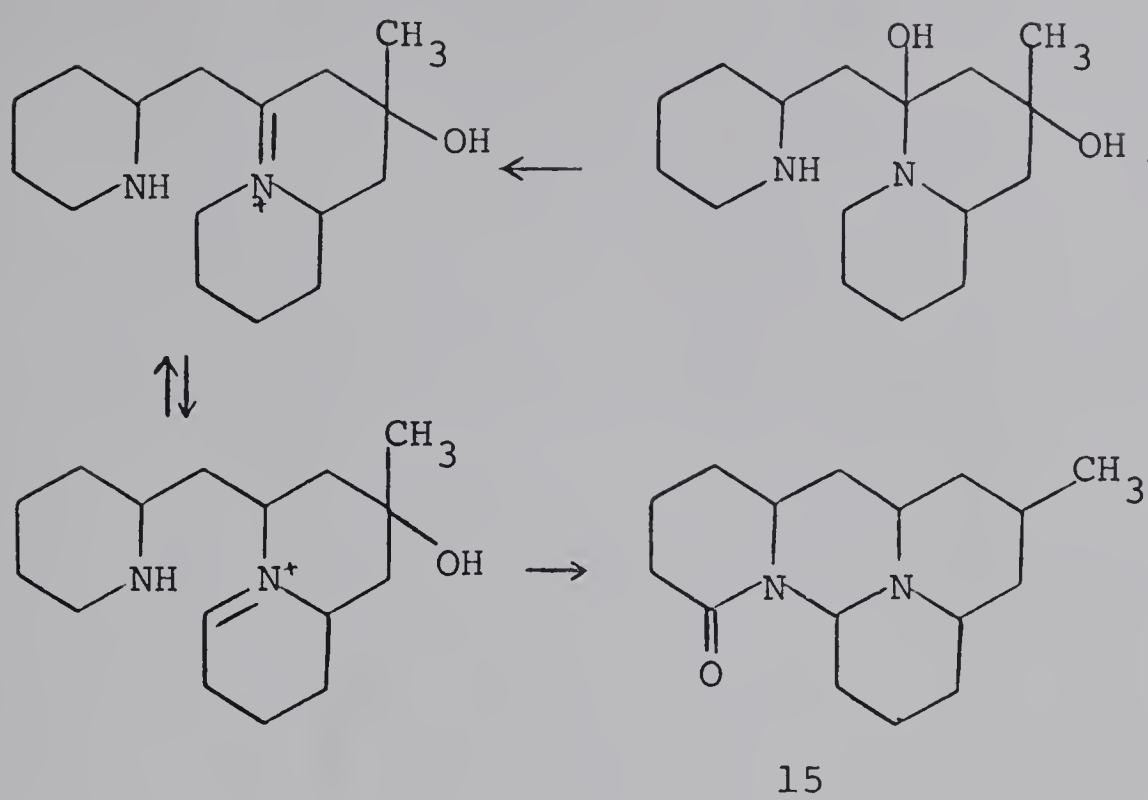


SCHEME 15B





SCHEME 15B (cont.)







### The Minor Alkaloids of L.Cernuum

An investigation of the minor alkaloids of Lycopodium cernuum L. was carried out by combining the various fractions obtained from chromatographic separations of cernuine and lycocernuine into those more polar than cernuine and those less polar than cernuine (those with lower  $R_f$  value and those with higher  $R_f$  value). The alkaloids isolated are discussed generally in order of increasing



polarity as obtained by column and/or by preparative thin layer chromatography. The purity of each of the alkaloids, as observed by tlc, is estimated to be >90%, unless otherwise mentioned. All molecular ion compositions were determined by high resolution mass spectrometry. In most cases the structures were not determined and speculation is kept to a minimum.

First the properties of the bases less polar (higher  $R_f$  value) than cernuine will be discussed.

Bases A were isolated as a mixture in the ratio 7:3. Intense absorption in the infrared ( $\text{CCl}_4$ ) at  $1755 \text{ cm}^{-1}$  indicated perhaps an ester or lactone function. Lack of sufficient material prevented further characterization of this mixture.

Base B showed a molecular ion at  $m/e$  248(20), identical with that of dihydrodeoxycernuine. A tlc comparison indicated it to be less polar than dihydrodeoxycernuine. A comparison of the mass spectrometric fragmentation pattern of Base B with that of dihydrodeoxycernuine in Table 4 indicated that Base B may be a stereoisomer of dihydrodeoxycernuine.

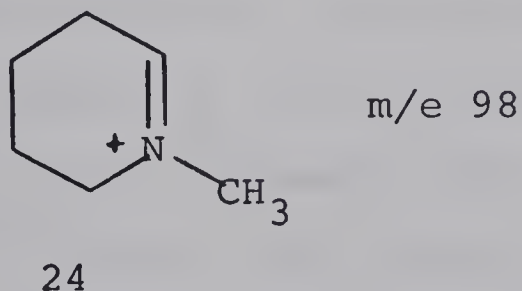


TABLE 4

<u>Base B</u>	<u>Dihydrodeoxycernuine</u>
m/e 248 (20)	m/e 248 (46)
247 (39)	247 (36)
220 (20)	220 (30)
219 (100)	219 (100)
206 (23)	206 (91)
205 (40)	205 (96)

Base C was shown to be identical in infrared spectrum and thin layer behavior with dihydrodeoxycernuine.

Base D did not show a recognizable molecular ion in the mass spectrum, however an intense fragment at m/e 98(100) was present which may correspond to the fragment 24.



Base E showed an apparent molecular ion at m/e 295(91) with the composition  $C_{19}H_{21}NO_2$ . Its infrared spectrum ( $CCl_4$ ) indicated absorption at 3080-3020  $cm^{-1}$  typical of unsaturation. Carbonyl, NH and OH absorption was not observed. The



ultraviolet spectrum showed a maximum in both neutral and acidic media at 270 m $\mu$ . The nmr spectrum showed singlets at  $\tau$ 6.2 and 6.4 attributable perhaps to two O-CH<sub>3</sub> functions, a singlet at  $\tau$ 7.50 typical of either an N-CH<sub>3</sub> function or a methyl on an aromatic ring and another singlet at  $\tau$ 8.77 due presumably to the presence of a tertiary methyl group. The chemical shift of the methyl group would indicate it is in the vicinity of an unsaturated function, the presence of which is indicated by two low field signals at  $\tau$ 1.7 and 3.5.

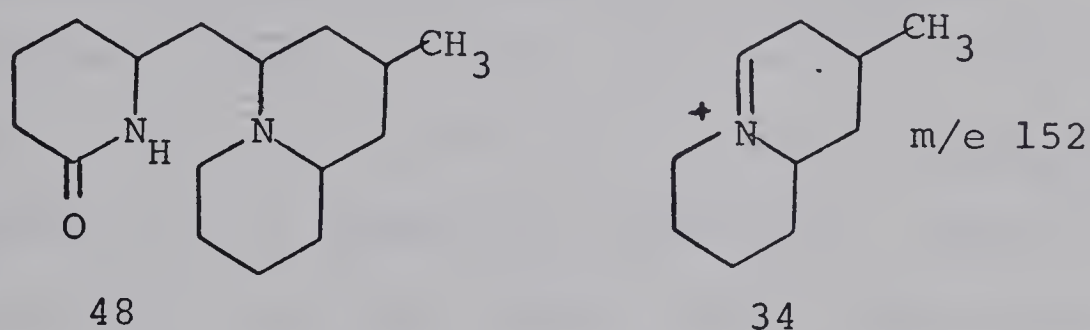
Base F showed a molecular ion at m/e 309(2) with the composition C<sub>21</sub>H<sub>27</sub>NO. The infrared spectrum indicated absorption at 3090-3010 cm<sup>-1</sup> typical of unsaturation but the uv spectrum did not show a maximum above 215 m $\mu$ . No carbonyl, NH or OH absorption was observed in the infrared. The nmr spectrum indicated a low field complex at  $\tau$ 2.5-3.0 and a multiplet centered at  $\tau$ 3.4 in agreement with the unsaturation observed in the ir. Two singlets at  $\tau$ 7.73 and 8.8, due presumably to N-CH<sub>3</sub> and C-CH<sub>3</sub>, were buried in complex multiplets which made integration difficult, thus the exact number of low field protons was not determined.





The results of the investigation into the nature of the bases obtained from material more polar (lower  $R_f$ ) than cernuine will now be discussed.

Base G showed a molecular ion at m/e 264(2). The fact that the base peak was observed at m/e 152(100) indicated that this substance might be a dihydrocervuine 48 and the fragment might be 34.



A comparison of the mass spectrum of Base G with that of the hydrogenolysis product of anhydrolycerceraine\*, (identical in structure with 48 but not necessarily in stereochemistry) as shown in Table 5, indicated the fragmentation mode to be very similar.

TABLE 5

<u>Base G</u>	<u>Anhydrolycocernuine Hydrogenolysis Product</u>
m/e 264 (2)	m/e 264 (3)
152 (100)	152 (100)
110 (23)	110 (16)

\* S.Valverde-Lopez, Ph.D. Thesis, U. of A., 1966.



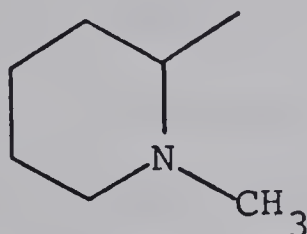
Both compounds showed in the infrared ( $\text{CHCl}_3$ ) a maximum at  $3400\text{ cm}^{-1}$  typical of NH absorption, however in the carbonyl region Base G absorbed strongly at  $1750$ ,  $1680$  and  $1660\text{ cm}^{-1}$ , incompatible with the structure of the hydrogenolysis product which absorbed only at  $1645\text{ cm}^{-1}$ .

Base H, mp  $145-147^\circ$ , exhibited a molecular ion at  $m/e\ 354(95)$  with the composition  $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3$ . Acetylation yielded a product which showed a molecular ion at  $m/e\ 394(4)$  with the composition  $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_4$  corresponding to a monoacetyl derivative. Base H in its infrared spectrum ( $\text{CHCl}_3$ ) showed absorption at  $3610$ ,  $3470$  and  $3440\text{ cm}^{-1}$  with carbonyl absorption at  $1715\text{ cm}^{-1}$  while the infrared spectrum ( $\text{CCl}_4$ ) of the acetylated product showed absorption at  $3475$  and  $3380\text{ cm}^{-1}$  with carbonyl absorption at  $1740$  and  $1715\text{ cm}^{-1}$ . These observations are in agreement with the acetylation of an OH function ( $3610\text{ cm}^{-1}$ ). The nmr spectrum of Base H showed a multiplet at  $\tau 2.25-3.3$  indicating unsaturation, a doublet at  $\tau 5.9$ , and a singlet at  $\tau 6.46$  indicative of an  $-\text{OCH}_3$  group. Based on the integration of the peak at  $\tau 6.46$  being equal to three protons, the proton ratios are approximately 8:2:3.

Base I showed an apparent molecular ion at  $m/e\ 278(11)$  with composition  $\text{C}_{17}\text{H}_{30}\text{N}_2\text{O}$ . Acetylation

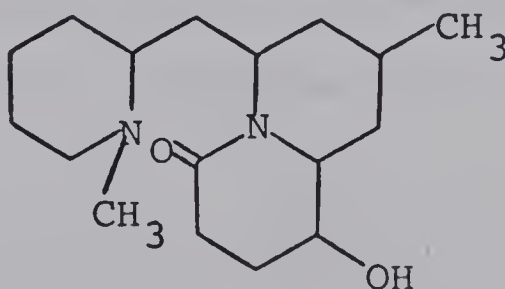


of this base yielded a mixture of products (tlc), the mass spectrum of which showed an appar. mol. ion at  $m/e$  320(5), indicative of monoacetylated mixture. In the mass spectra of the unacetylated and acetylated Base I, the base peaks were observed at  $m/e$  98(100). An exact mass measurement on the  $m/e$  98 fragment from Base I indicated it to have composition  $C_6H_{12}N$  which probably arises from



49

part structure 49 in the base. The infrared spectrum ( $CHCl_3$ ) of Base I showed typical OH absorption at 3590 and 3400  $cm^{-1}$  and a band at 1660-1620  $cm^{-1}$  typical of a lactam carbonyl while the acetylated mixture showed absorption in the infrared ( $CCl_4$ ) at 1760 and 1660  $cm^{-1}$ . A structure such as 50 is compatible with the evidence but no definite proof has been obtained.



50



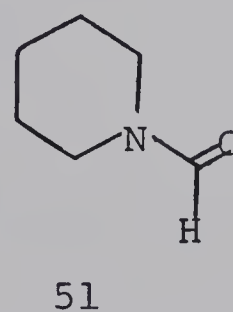
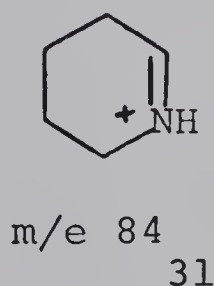
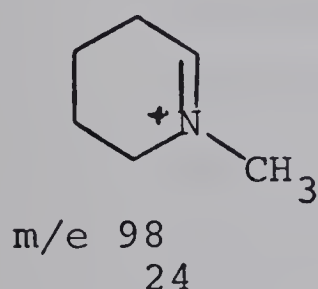
Base J had a molecular ion at  $m/e$  264(23) and when acetylated it yielded a product which showed a molecular ion at  $m/e$  306(10) consistent with the formation of a monoacetyl derivative. The infrared spectrum of Base J showed absorption at 3680, 3600 and  $3400\text{ cm}^{-1}$  indicative of an OH group, and at  $1680\text{ cm}^{-1}$ . The acetylated compound showed absorption at 1735 and  $1675\text{ cm}^{-1}$ . The carbonyl was not reduced with  $\text{NaBH}_4$  (and hence is probably not ketonic), while with  $\text{LiAlH}_4$  a product was obtained, the ir spectrum of which did not show carbonyl absorption.

Base K showed an apparent molecular ion at  $m/e$  278(15) with the composition  $\text{C}_{17}\text{H}_{30}\text{N}_2\text{O}$ . The infrared spectrum showed absorption at  $3370\text{ cm}^{-1}$  and at  $1670\text{ cm}^{-1}$ . Acetylation yielded a product which showed absorption in the infrared ( $\text{CCl}_4$ ) at 1740 and  $1680\text{ cm}^{-1}$  consistent with O-acetylation. When Base K was treated with  $\text{LiAlH}_4$  a product was obtained which showed a molecular ion at  $m/e$  264(2) with the composition  $\text{C}_{17}\text{H}_{32}\text{N}_2$ . This product did not show carbonyl absorption in the infrared. Basic hydrolysis of Base K yielded a product which showed a molecular ion at  $m/e$  250(10)





corresponding to the loss of 28 molecular weight units which could be the loss of the C=O function. An infrared spectrum on the hydrolysis product did not show carbonyl absorption. The behavior of Base K on hydride reduction and hydrolysis suggests the presence of an N-formyl group. Some support for this possibility comes from the mass spectra of the hydride and hydrolysis products which show base peaks at m/e 98 with the composition  $C_6H_{12}N$  and m/e 84 with the composition  $C_5H_{10}N$ , respectively. These may be attributed to the following two fragments which arise from the partial



structure 51 for Base K. Provided Base K is indeed a single compound and possesses both an N-formyl and a hydroxyl group, the molecular formula must be in fact  $C_{17}H_{32}N_2O_2$  and the "apparent molecular ion" must arise by facile loss of water from the actual molecular ion. Because of lack of material, a combustion analysis was not performed, and the structure was not further investigated.



Base L showed a molecular ion at  $m/e$  262(100). It was obtained by acetylating a mixture of very polar alkaloids, chromatographing the acetylated material (ir ( $\text{CCl}_4$ ) 1740 and  $1675\text{ cm}^{-1}$ ), then hydrolyzing. The infrared spectrum ( $\text{CCl}_4$ ) showed absorption at  $1680\text{ cm}^{-1}$  but did not show any OH absorption. A tlc comparison indicated this alkaloid was not identical with cernuine. A comparison of mass spectra (Table 6) also indicated this to be the case.

TABLE 6

<u>Base L</u>	<u>Cernuine</u>
$m/e$ 262(100)	$m/e$ 262(64)
233(98)	233(100)
220(94)	220(92)
219(50)	219(49)
152(24)	152(5)
98(30)	98(10)

Base M showed an apparent molecular ion at  $m/e$  320(10). The infrared spectrum of Base M showed absorption at 1730, 1670 and  $1640\text{ cm}^{-1}$  typical of O-acetyl, lactam and N-acetyl groupings. The two major fragments in the mass spectrum of Base M at  $m/e$  208(100) and  $m/e$  84(80) resemble the major fragments in the mass spectra of the Base K acetylation and hydrolysis products. Both acetylated Base K



and Base M showed a base peak at  $m/e$  208(100) indicating this fragment may be derived from the same part structure. The Base K hydrolysis product showed a base peak at  $m/e$  84(100) which is also a major peak in Base M. No further work was done on investigating the minor alkaloids of L. cernuum L.



## EXPERIMENTAL

Nuclear magnetic resonance spectra were measured on a Varian Associates model A-60 or HR-100 spectrometer using tetramethylsilane as an internal standard. The signals are described as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; c = complex series of peaks.

Infrared spectra were recorded on a Perkin-Elmer model 421 dual grating or a Perkin-Elmer model 337 grating infrared spectrophotometer.

Ultraviolet spectra were measured on a Perkin-Elmer model 202, a Cary model 14M, or a Jasco model ORD/UV-5 spectrophotometer using 95% ethanol as solvent.

Mass spectra were recorded on an A.E.I. model MS-2H or an A.E.I. model MS-9 mass spectrometer and are recorded as a percentage of the most intense peak. Unless otherwise noted, the spectra were determined at 70 eV at a temperature between 185-200°.

Melting points were determined on a hot-stage Fisher-Johns melting point apparatus and are uncorrected.

Microanalyses were performed by C. Daesslé, Montreal; F. Pascher, Bonn, Germany, who also carried out the pKa determination and by Mrs. D. Mahlow,





U. of A. Chemistry Department.

Alumina refers to Fischer Adsorption Alumina or British Drug Houses Alumina of activity III-IV (Brockmann scale). Silica gel refers to B.D.H. Chromatographic Adsorption Silica Gel.

Thin layer chromatograms were carried out on microslides, unless otherwise specified, prepared from Alumina G or Silica Gel G (Research Specialties Co., Richmond, California), and were developed in an iodine chamber or with Dragendorff's reagent<sup>84</sup>.

Skellysolve B refers to Skelly Oil Company light petroleum bp 62-70°.

Gas chromatographic separations were carried out on a Varian Aerograph Autoprep 700.

All small scale evaporative distillations (1 mg - 1 g) were carried out in a glass tube sealed at one end and connected at the other end directly to the vacuum line. The tube and contents were placed in an aluminum block, and the temperature of the block raised until the product distilled to a cooled region outside of the block.



## EXPERIMENTAL

## SECTION ONE

1. Isolation of Cernuine and Lycocernuine

21Kg of dried, finely ground L. cernuum (collected in Mexico), was extracted in 2-3Kg batches. Each lot was stirred at room temperature with methanol (2-3ℓ) for 24 hr and filtered, and the methanol extract concentrated under reduced pressure. This process was repeated twice and the combined extracts were then warmed with 3% aq tartaric acid (0.5-1ℓ). The tartaric acid insoluble portion was removed by filtration and then extracted again with tartaric acid (0.5-1ℓ). The combined filtrates were extracted with ether, made strongly basic with conc  $\text{NH}_4\text{OH}$ , and extracted with  $\text{CHCl}_3$ . Evaporation of the chloroform yielded 8g of crude bases. Crystallization from acetone yielded 2.7g of lycocernuine which after one recrystallization from acetone (2.1g) had mp 230-231°.

The mother liquors from the crystallization were dissolved in benzene and chromatographed over alumina (200g, 200 ml fractions). Elution with benzene, ether and ether -  $\text{CHCl}_3$  (15:1) gave a mixture of minor bases (0.16g). Elution with ether -  $\text{CHCl}_3$  (1:1) gave cernuine



(0.95g). Elution with  $\text{CHCl}_3$  first gave a 1:1 mixture of cernuine-lycocernuine (0.3g). Continued elution gave lycocernuine (0.8g). Elution with  $\text{CHCl}_3\text{-CH}_3\text{OH}$  (5:1) gave a mixture of minor bases (2.1g).

Cernuine was further purified by sublimation at  $100^\circ$  (0.05 mm): mp  $103\text{-}104^\circ$ ;  $[\alpha]_D -20.5^\circ$  (c, 0.1 in  $\text{CH}_3\text{OH}$ ); ir ( $\text{CCl}_4$ )  $1640$  (lactam  $\text{C=O}$ ),  $1415$  ( $\text{CH}_2$   $\alpha$  to  $\text{C=O}$ )  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau 4.53$  (q, 1,  $J=11$  and  $2.5$  cps,  $\text{N-CH-N}$ ),  $6.3\text{-}7.1$  (c, 3,  $\text{N-CH}$ ),  $7.55\text{-}7.80$  (m, 2,  $\text{-CH}_2\text{-C=O}$ ),  $9.14$  (d, 3,  $J=6$  cps,  $\text{CH}_3\text{-CH}$ ); mass spectrum  $m/e$   $262(\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}, 49)$ ,  $261(15)$ ,  $247(15)$ ,  $234(26)$ ,  $233(100)$ ,  $221(16)$ ,  $220(91)$ ,  $219(57)$ ,  $205(28)$ ,  $191(24)$ ,  $178(15)$ ,  $164(20)$ ,  $151(21)$ ,  $150(20)$ .

The minor bases will be referred to later in the experimental section.

## 2. Cernuine Methiodide

Cernuine (50mg) was dissolved in  $\text{CH}_3\text{OH}$  (2-3 ml) and 0.75 ml of  $\text{CH}_3\text{I}$  was added. The mixture was heated at reflux for 5 hr, the solvent evaporated under reduced pressure and the residue washed with ether. Crystallization from acetone and recrystallization from acetone with a trace of ether yielded white crystals which were dried in vacuo at the reflux temperature of benzene : mp  $237\text{-}237.5^\circ$ ; ir (Nujol)  $3520$ ,  $3400$ ,  $1645$ ,  $1623$   $\text{cm}^{-1}$ .



Anal. Calcd. for  $C_{16}H_{26}N_2O \cdot CH_3I$ : C, 50.50; H, 7.23; N, 6.93. Found : C, 50.21; H, 7.52; N, 6.51.

### 3. Cernuine Perchlorate

Cernuine (20mg) was dissolved in  $CH_3OH$  (1 ml) containing 1 drop of 70%  $HClO_4$ . Water (1 ml) was added, the  $CH_3OH$  boiled off. The crystals obtained from the aqueous solution were recrystallized from  $H_2O$  and dried under vacuum at the reflux temperature of benzene : colorless crystals, mp 100-105°; ir (Nujol) 3460, 1648, 1625  $cm^{-1}$ .

### 4. Dihydrodeoxycernuine (18)

Cernuine (54mg, 0.2 mmol), dissolved in ether (20 ml) was heated under reflux with a slurry of  $LiAlH_4$  (111mg, 3.9 mmol) for 20 hr. The reaction mixture was worked up by the method of Mićović and Mahailović<sup>119</sup> yielding 43mg (86%) of material which was purified by evaporative distillation (bath temperature 80-120°, 0.05 mm) : mp 63.5-65°; pK<sub>a</sub> (80% Methyl Cellosolve) 6.90, 8.55; ir ( $CCl_4$ ) 2810, 2725, 2660  $cm^{-1}$ , no lactam carbonyl or 1412  $cm^{-1}$  absorption; nmr ( $CCl_4$ )  $\tau$ 6.40 (q, 1,  $J=11$  and 2.5 cps,  $N-CH-N$ ), 6.73-7.85 (c, 5,  $CH-N$ ), 9.15 (d, 3,  $J=5.5$  cps,  $CH_3-CH$ ); mass spectrum m/e 248 ( $C_{16}H_{28}N_2$ , 46), 247(35), 233(19), 220(26), 219(100), 206(89), 205(80),





177(25), 164(24), 152(16), 151(39), 150(49), 138(17),  
137(23), 136(66), 122(12), 110(15).

Anal. Calcd. for  $C_{16}H_{28}N_2$  : C, 77.36; H, 11.38.

Found : C, 77.22; H, 11.09.

##### 5. Dehydrogenation of Cernuine, 200°

Cernuine (50mg), 5% Pd/C (150mg) and freshly distilled tetralin (1 ml) were heated in a sealed tube at 200° for five days. The cooled reaction mixture was diluted with ether, the catalyst filtered off and washed well with ether and then a little methanol, and the filtrate extracted with dil hydrochloric acid. The aq extract was washed with ether, made basic with conc  $NH_4OH$  and extracted with  $CHCl_3$ . The dried ( $MgSO_4$ ), filtered, and evaporated extract yielded 22mg of product. The dehydrogenation was repeated on a second 50mg sample of cernuine.

The total basic material (44mg) was chromatographed on alumina (1.5g, 25 ml fractions).

Elution with benzene and benzene-ether (3:2): 25mg; tlc -  $Al_2O_3$ (ether) - at least twelve components all less polar (higher  $R_f$  value) than cernuine; uv max (EtOH) 265-262 m $\mu$ ; uv max (EtOH,  $H^+$ ) 270-269 m $\mu$ .

Elution with ether -  $CHCl_3$  (3:2) and  $CHCl_3$  : 16mg; tlc -  $Al_2O_3$ ( $CHCl_3$ ) - two major components, more polar



than cernuine. Further purification was carried out by ptlc (alumina, 0.75 mm layers,  $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 99:1).

Less polar component, 16: 4.5mg; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 99:1) - homogeneous; uv max (EtOH) 262 m $\mu$ ; uv max (EtOH,  $\text{H}^+$ ) 268 m $\mu$ ; mass spectrum m/e 260(12), 218(34), 217(21), 164(17), 163(100), 149(29), 134(15), 125(12), 123(16), 121(34), 120(17), 111(22), 109(22), 107(12), 98(21), 97(34), 96(12), 95(32), 85(25), 83(36), 81(32).

More polar component, 17: 5.5mg; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 99:1) - homogeneous; ir (Nujol) 3460, 3180, 3050, 1663 (amide I), 1620 (amide II), 1560  $\text{cm}^{-1}$ ; uv max (EtOH) 264 m $\mu$  ( $\epsilon$ 4300); uv max (EtOH,  $\text{H}^+$ ) 265 m $\mu$  ( $\epsilon$ 7800); mass spectrum m/e 262(1), 247(5), 233(8), 229(8), 220(40), 218(5), 216(7), 215(13), 204(15), 203(7), 190(18), 176(18), 175(6), 174(6), 164(8), 163(100), 161(7), 160(8), 147(14), 146(11), 134(26), 133(17), 121(40), 120(18).

## 6. Dehydrogenation of Cernuine, 300°

Cernuine (100mg), 5% Pd/C (300mg), and freshly distilled tetralin (3 ml) were heated in a sealed tube at 300° for 7 days. The cooled reaction mixture was worked up in a similar manner to that used for the previous dehydrogenation and yielded 60mg of basic material which was purified by ptlc (0.75 mm



alumina layers, Skellysolve B - benzene, 2:3).

Higher  $R_f$  value components: 30mg; tlc -  $Al_2O_3$  (Skellysolve B - benzene, 2:3) - two components.

Lower  $R_f$  value components: 17mg; tlc -  $Al_2O_3$  (Skellysolve B - benzene, 2:3) - at least five components.

Further ptlc (alumina) on the less polar (higher  $R_f$  value ) components yielded:

Product A: 11mg, a semi-solid purified by evaporative distillation ( $135^\circ$ , 0.05 mm); tlc -  $Al_2O_3$  (Skellysolve B - benzene, 2:3) -  $SiO_2$  ( $CH_3OH$ ) - homogeneous; ir ( $CCl_4$ ) 3080-3030,  $1595\text{ cm}^{-1}$ ; uv max (EtOH) 280(sh), 272 ( $\epsilon 1340$ ), 268-247(sh)  $m\mu$  ( $\epsilon 1260$ ); uv max (EtOH,  $H^+$ ) 297 ( $\epsilon 1260$ ), 274 ( $\epsilon 1900$ ), 247(sh)  $m\mu$  ( $\epsilon 950$ ); nmr ( $CCl_4$ )  $\tau 1.98$ -2.07 (c, 1,  $\alpha$  proton on py ring), 2.55-2.65 (c, 2,  $\delta CH$  on py ring), 3.09 and 3.19 (m and s, 2), 7.0-7.3 (c, 3, "benzylic" protons), 7.63 and 7.69 (two s, 3), 8.0-8.8 (c, 16-18), 8.9-9.2 (c, 4); mass spectrum m/e 231(6), 230(9), 216(11), 202(29), 196(16), 190(20), 189(100), 176(40).

Product B, 7: 12mg, an oil purified by evaporative distillation ( $135^\circ$ , 0.05 mm); tlc -  $Al_2O_3$  (Skellysolve B - benzene, 1:3) - homogeneous; ir ( $CCl_4$ ) 3060-3000,  $1693\text{ cm}^{-1}$ ; uv max (EtOH) 271 ( $\epsilon 2200$ ), 268 ( $\epsilon 2300$ ), 264  $m\mu$  ( $\epsilon 2500$ ); uv max (EtOH,  $H^+$ ) 268  $m\mu$



( $\epsilon$ 5400); nmr ( $\text{CCl}_4$ )  $\tau$ 3.19 (s, 2), 7.13-7.36 (c, 4), 7.69 (s, 3), 8.2-8.8 (c, 10), 9.0-9.15 (c, 6); mass spectrum m/e 219(2), 218(6), 204(15), 191(13), 190(38), 177(61), 176(17), 164(13), 163(100), 134(20), 133(12), 121(23), 120(18).

### 7. Synthesis of 2-n-Butyl-4-methylpyridine

2-n-Butyl-4-methylpyridine (6g) was prepared according to reference 74. The distilled product was filtered through an alumina column (pentane) to remove a polar impurity : tlc -  $\text{Al}_2\text{O}_3$  (benzene) - homogeneous; uv max (EtOH) 266 ( $\epsilon$ 2460), 259 m $\mu$  ( $\epsilon$ 2890); uv max (EtOH,  $\text{H}^+$ ) 262 m $\mu$  ( $\epsilon$ 6600); nmr ( $\text{CCl}_4$ )  $\tau$ 1.72 (q, 1, J=5 and 1 cps,  $\alpha$  proton on py ring), 3.08 (d, 1, J=1 cps,  $\beta$  proton), 3.18 (q, 1, J=5 and 1 cps,  $\beta$  proton), 7.15-7.5 (c, 2, "benzylic" protons), 7.72 (s, 3,  $\gamma$   $\text{CH}_3$  on py ring), 8.0-8.9 (c, 4), 8.9-9.1 (t, 3,  $\text{CH}_3$ - $\text{CH}_2$ ); mass spectrum, m/e 149(1), 148(3), 134(16), 121(5), 120(25), 106(100), 105(5), 93(5), 92(5), 77(5), 43(40).

### 8. Synthesis of 2-n-Butyl-4-methyl-6-n-pentylpyridine(7)

2-n-Butyl-4-methylpyridine (2g, 0.0134 mol) in dry toluene (50 ml) was added dropwise, with stirring, to a solution of 2 equivalents of pentyllithium in ether (150 ml). The ether was distilled from the







dark-red solution, the resulting solution kept at 110° for 9 hr, the solution cooled in an ice bath, and water added cautiously followed by dil hydrochloric acid. The aqueous acidic layer was extracted again with dil hydrochloric acid, and the combined aqueous extracts made alkaline with conc  $\text{NH}_4\text{OH}$  and extracted with  $\text{CHCl}_3$ . Evaporation of the dried ( $\text{MgSO}_4$ ), filtered, chloroform solution yielded a mixture (2.0g) of starting material and product which was separated by chromatography over alumina (70g, 20 ml fractions). The fraction eluted with benzene contained the desired product (1.1g, 37%); bp 140-145° (bath temperature, 1.5 mm); tlc -  $\text{Al}_2\text{O}_3$  (benzene) - homogeneous; ir ( $\text{CCl}_4$ ) 3040, 2960, 2925, 2860, 1605, 1570, 1460, 1380, 855  $\text{cm}^{-1}$ ; uv max (EtOH) 271.5 ( $\epsilon$ 3500), 268 ( $\epsilon$ 3800), 264  $\text{m}\mu$  ( $\epsilon$ 4000); uv max (EtOH,  $\text{H}^+$ ) 268  $\text{m}\mu$  ( $\epsilon$ 9000); nmr ( $\text{CCl}_4$ )  $\tau$ 3.19 (s, 1), 7.22 (c, 4), 7.69 (t, 3,  $J=0.5$  cps), 8.10-8.85 (c, 10), 8.95-9.20 (c, 6,  $\text{CH}_3\text{-CH}_2$ ); mass spectrum m/e 219(3), 218(6), 204(19), 191(7), 190(38), 178(10), 177(71), 176(18), 164(13), 163(100), 148(6), 147(9), 146(7), 135(10), 134(30), 133(12), 121(33), 120(21), 107(21), 91(6), 79(7), 77(11).

The chloroplatinate, prepared in the usual manner<sup>105b</sup> and recrystallized from ethanol containing



a drop of hydrochloric acid, formed orange crystals, mp 189-190°.

Anal. Calcd. for  $(C_{15}H_{25}N)_2 \cdot H_2PtCl_6$ : C, 42.46; H, 6.18. Found: C, 42.24; H, 6.05.

### 9. Dehydrogenation of Dihydrodeoxycernuine

An intimate mixture of dihydrodeoxycernuine (0.1g) and powdered selenium (0.3g) was heated at 300° in a sealed tube for 24 hr. The volatile components in the tube were distilled under vacuum from the selenium (extraction with benzene in a Soxhlet apparatus was also used on occasion), the distillate dissolved in benzene and extracted with several portions of dil hydrochloric acid. The combined aqueous extracts were made alkaline with conc  $NH_4OH$  and extracted with ether. The residue (45mg) from the ether contained two major components (tlc) which were separated by ptlc (0.75 mm alumina layers, benzene-ether, 9:1).

Less polar component 8 : 6mg; tlc -  $Al_2O_3$  (benzene) - homogeneous; uv max (EtOH) 271.5 ( $\epsilon$ 3550), 268 ( $\epsilon$ 3850), 264  $m\mu$  ( $\epsilon$ 4100); uv max (EtOH,  $H^+$ ) 269  $m\mu$  ( $\epsilon$ 9500); mass spectrum m/e 233(3), 232(5), 218(15), 204(25), 192(6), 190(26), 177(9), 176(24), 164(13), 163(100), 148(12), 146(8), 135(15), 134(50), 133(14), 121(34), 120(16), 107(7), 91(5), 79(6), 77(10), 191(45).



More polar component 11: 3mg; tlc -  $\text{Al}_2\text{O}_3$  (benzene-ether, 8:2) - one major component; uv max (EtOH) 316, 303, 268(sh), 262, 227  $\text{m}\mu$ ; uv max (EtOH,  $\text{H}^+$ ) 316, 305(sh), 266, 238  $\text{m}\mu$ ; mass spectrum  $m/e$  169(22), 156(100), 133(23), 120(31), 119(51), 92(70).

10. Attempted Syntheses of 2- $[\alpha$ -picolyl]-4-methylquinoline (11)

$\alpha$ -Picoline (11g, 0.175 mol) was added dropwise to a stirred ether solution (200 ml) containing 2 equivalents of phenyllithium. The mixture was stirred for 1.5 hr, then a solution of 4-methylquinoline (25g, 0.175 mol) in toluene (25 ml) was added dropwise. The mixture was diluted with 100 ml of toluene, the ether distilled off and the resulting solution kept at  $110^\circ$  for 9 hr, then cooled to  $90^\circ$  and air bubbled through for 4 hr. The cooled solution was diluted with ether, ice added, and extracted with dil hydrochloric acid. The aqueous extract was made alkaline with NaOH pellets and extracted with  $\text{CHCl}_3$ . The major component of the residual oil was identified (tlc) as 4-methylquinoline.

2,4-Dimethylquinoline (1g, 0.0064 mol) dissolved in ether (30 ml) was added dropwise (15 min) under  $\text{N}_2$  to an etherial solution (150 ml) containing 2 equiva-





lents of phenyllithium. After addition was complete the solution was stirred for 1 hr, pyridine (3g, 0.038 mol) dissolved in ether (50 ml) added dropwise and stirring continued for a further 0.5 hr. The solution was diluted with dry dimethoxyethane (100 ml) and the ether distilled from the mixture which was kept at 79° for 3 hr after which the solvent was removed under reduced pressure and the residual oil diluted with ether. Ice was added, the mixture extracted with dil hydrochloric acid, the acidic extracts made alkaline with NaOH pellets then extracted with  $\text{CH}_2\text{Cl}_2$ . The residual oil after distillation and chromatography on alumina and examination of the fractions did not show the expected product. 2,4-Dimethylquinoline was recovered in good yield.

#### 11. Further Synthetic Attempts Toward 11

To a solution of freshly distilled (100-110°, 0.1 mm)  $\delta$ -valerolactam (20g, 0.2 mol) in  $\text{CH}_2\text{Cl}_2$  (200 ml) was added triethyloxonium fluoroborate (43g, 0.25 mol), prepared by the method of Meerwein<sup>76</sup>, dissolved in  $\text{CH}_2\text{Cl}_2$  (50 ml). The mixture was stirred at room temperature for 4 hr then poured into an aq  $\text{K}_2\text{CO}_3$  solution and extracted with  $\text{CH}_2\text{Cl}_2$ . The





dried ( $\text{MgSO}_4$ ), filtered and evaporated extract yielded 20g (80%) of the valerolactam imino ether which was distilled ( $90-110^\circ$ , 20-25 mm).

The ethyl imino ether (10g, 0.078 mol), dissolved in ether (15 ml), was added dropwise to a solution of 2-lithiomethyl-4-methylquinoline (0.025 mol; prepared from 4g of 2,4-dimethylquinoline and 2 equivalents of phenyllithium) in ether (30 ml), and stirred for 40 hr. The solution was diluted with dimethoxyethane (150 ml) and the ether distilled from the mixture which was kept at  $78^\circ$  for 2 hr, after which the solvent was removed under reduced pressure, the residual oil diluted with ether and poured into an aq  $\text{K}_2\text{CO}_3$  solution. Extraction with ether yielded 14.5g of material which was chromatographed on alumina (400g, 400 ml fractions), however only partial purification was achieved. Careful evaporative distillation separated the 2,4-dimethylquinoline (bath temp  $<90^\circ$ , 0.08 mm) from the olefin 13 ( $130-170^\circ$ , 0.07 mm), a viscous yellow oil (1.1g, 18%): tlc -  $\text{SiO}_2$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 95:5) - two basic components, a neutral impurity; ir ( $\text{CCl}_4$ )  $3070-3025$ ,  $1640$ ,  $1600\text{cm}^{-1}$ ; uv max (EtOH) 327 ( $\epsilon 5950$ ), 316 ( $\epsilon 6710$ ), 310 ( $\epsilon 5180$ ), 303 ( $\epsilon 4830$ ), 285 ( $\epsilon 8550$ ), 277  $\text{m}\mu$ ; ( $\epsilon 8090$ ; uv max (EtOH,  $\text{H}^+$ ) 318 ( $\epsilon 8100$ ) 305 ( $\epsilon 6850$ ), 285  $\text{m}\mu$  ( $\epsilon 5340$ ); nmr ( $\text{CCl}_4$ )  $\tau 2.3-3.1$



(c, 4, aromatic protons), 3.4 (d, 1,  $J=0.5$  cps), 5.3 (s, 1), 6.6-6.8 (m, 2,  $\text{CH}_2\text{-N}$ ), 7.2-8.0 (c, 2, allylic  $\text{CH}_2$ ), 7.6 (d, 3,  $J=0.5\text{-}1$  cps), 8.0-8.6 (c, 4); mass spectrum  $m/e$  238(7), 237(34), 220(100), 208(50), 194(26), 160(64), 158(40), 157(28).

Hydrogenation of the olefin 13 (0.9g, 0.0038 mol) was carried out in  $\text{CH}_3\text{OH}$  (50 ml) containing 5% Pd/C (200mg) at atmospheric pressure and room temperature for 13 hr. The residue (0.82g), after removal of the catalyst by filtration and evaporation of the solvent, was chromatographed on alumina (30g, 100 ml fractions). Product 14 eluted with ether,  $\text{CH}_2\text{Cl}_2$  and  $\text{CHCl}_3$ , and was purified by evaporative distillation (bath temp 150-170°, 0.07 mm) yielding a viscous oil (0.28g, 31%): tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3\text{-CH}_3\text{OH}$ , 97:3) - homogeneous; ir ( $\text{CCl}_4$ ) 3300, 3050, 3025, 1600, 1555, 1500  $\text{cm}^{-1}$ ; uv max (EtOH) 316 ( $\epsilon$ 7200), 303 ( $\epsilon$ 6340), 278  $m\mu$  ( $\epsilon$ 8920); uv max (EtOH,  $\text{H}^+$ ) 317 ( $\epsilon$ 16800), 308  $m\mu$  ( $\epsilon$ 11500); nmr ( $\text{CCl}_4$ )  $\tau$ 2.0-2.9 (c, 4), 3.07 (s, 1), 7.17 (broad s, 2, "benzylic" protons), 6.9-7.6 (c, 3), 7.43 (s, 3), 7.78 (broad s,  $\text{NH?}$ ), 8.1-8.8 (c, 6); mass spectrum  $m/e$  240(0.2), 157(100), 115(10), 83(14), 55(24).

The hydrogenated olefin, 14, was acetylated using acetic anhydride-pyridine (1:2) and worked up



in the usual manner. The product, purified by chromatography on alumina followed by evaporative distillation (170-190°, 0.06 mm), was obtained as a semi-crystalline oil: ir ( $\text{CCl}_4$ ) 3050, 1640(doublet), 1600, 1560, 1510  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\tau$ 1.8-2.8 (c, 4), 3.0 (broad s, 1, proton on py ring), 4.75 (m, 1, ?), 5.4 (m, 2, ?), 6.4-7.6 (c, 5), 7.34 and 7.36 (two s, 3,  $\text{CH}_3$ ), 8.08 and 8.12 (two s, 3,  $\text{CH}_3\text{-C=O}$ ), 8.0-8.6 (c, 6); mass spectrum m/e 282(19), 239(23), 157(28), 126(47), 84(100).

Dehydrogenation of the dihydro olefin, 14, (70mg) was attempted in tetralin (5 ml) containing 5% Pd/C (140mg) at 180° for 2 hr under an atmosphere of  $\text{N}_2$ . Work-up involving extraction of the basic material gave 38mg, the major product being 2,4-dimethylquinoline (tlc). Similarly, the quinoline was obtained from a sealed tube dehydrogenation at 250° for 1 hr. Investigation of the minor products by chromatography, then TLC, uv and mass spectrometry did not indicate the presence of the desired product. Dehydrogenation of the dihydro olefin (50mg) in the presence of selenium powder (90mg) in a sealed tube at 305° for 10 min also gave the quinoline.

Dehydrogenation of the olefin, 13, (40mg) was attempted with 5% Pd/C (40mg) in a sealed tube at





255° for 1 hr and yielded 18mg of product, mostly 2,4-dimethylquinoline. Similarly in the presence of selenium powder at 315° for 1 hr, the quinoline was the major product.

## 12. Hydrolysis of Cernuine

Cernuine (28mg), dissolved in a solution of 25% KOH in ethylene glycol (5 ml) was heated at 190° for 11 hr. The cooled reaction mixture was diluted with H<sub>2</sub>O and continuously extracted with ether for 55 hr. The aqueous layer was evaporated to dryness under reduced pressure, methanolic hydrochloric acid added to the residue, the solvent again evaporated and the residue dried at the vacuum pump for 4 hr. The residue was esterified with excess ethereal diazomethane, the ether solution extracted with H<sub>2</sub>O, dried, filtered and the filtrate evaporated yielding 19mg of residue which was chromatographed on alumina (0.7g, 10 ml fractions). Elution with ether - CHCl<sub>3</sub> (1:3) gave compound 19: 4.6mg; tlc - Al<sub>2</sub>O<sub>3</sub> (CHCl<sub>3</sub>-CH<sub>3</sub>OH, 99.5-0.5) - homogeneous; ir (CCl<sub>4</sub>) 1730 cm<sup>-1</sup>; mass spectrum m/e 295(10), 294(50), 293(73), 279(14), 266(19), 265(83), 262(15), 261(16), 252(61), 251(51), 237(13), 233(35), 221(16), 220(25), 219(18), 207(19), 206(28), 205(69), 194(26), 193(25), 192(28), 191(85), 179(23),





177(19), 166(25), 165(42), 164(25), 152(59), 151(49), 150(58), 137(22), 136(100), 123(16), 122(17), 110(32), 97(31).

### 13. Hydrogenolysis of Cernuine Methiodide

The methiodide (29mg), dissolved in  $\text{CH}_3\text{OH}$  (30 ml) with  $\text{PtO}_2$  (20mg) added, was subjected to hydrogenation at room temperature and 50 psi for 20 hr. The residue obtained, after filtration and evaporation of the solvent, was triturated with 50 ml of  $\text{CH}_3\text{OH}$ . The methanol solution was concentrated to give crystals which were recrystallized from acetone and dried under vacuum at the reflux temperature of benzene; white crystals, mp  $234-235^\circ$ ; ir (Nujol) 3510, 3490,  $1635\text{ cm}^{-1}$ .

### 14. Formic Acid-Formaldehyde Cleavage of Dihydrodeoxycernuine

Dihydrodeoxycernuine (130mg), dissolved in 3 ml of a 1:1 solution of 98% formic acid and 40% formaldehyde, was heated on the steam bath for 20 hr, then the solution was made alkaline with dil aq NaOH. The aqueous solution was extracted with  $\text{CHCl}_3$ , the extract dried ( $\text{MgSO}_4$ ), filtered and evaporated yielding a residue which contained at least four components (tlc). Purification was carried out by repeated ptlc



(alumina, 0.75 mm,  $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 99:1) followed by evaporative distillation:

Product 21: 40mg; ir ( $\text{CCl}_4$ ) 3630, 3320 (broad),  $2760\text{ cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\tau$ 5.35 (m, 2, not present when spectrum run in  $\text{CDCl}_3+\text{D}_2\text{O}$ ), 6.35 and 6.50 (two s, 4), 6.94-7.87 (c, 7,  $\text{CH-N}$  protons), 7.58 (s, 3), 7.87-8.8 (c), 9.01 (d, 3,  $J=3$  cps).

The acetonide of product 21 was prepared in the usual manner<sup>86</sup> and was purified by chromatography on alumina (1.0g). The product was eluted with ether: tlc -  $\text{Al}_2\text{O}_3$ (benzene) - homogeneous; mass spectrum m/e 364(7), 349(13), 278(9), 266(11), 252(43), 236(12), 190(26), 178(22), 160(17), 112(17), 111(22), 110(26), 98(100), 96(27).

Product 22: 7mg; mass spectrum m/e 336(7), 321(8), 291(6), 264(6), 250(11), 238(14), 237(14), 224(53), 222(17), 208(23), 112(19), 111(21), 110(19), 98(100), 97(19), 96(22).

Product 23: 7mg.

The acetylation product of 23 was prepared in the usual manner: ir ( $\text{CHCl}_3$ ) 2780, 1720,  $1025\text{ cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\tau$ 4.43 (m, 1, not present when spectrum run in  $\text{CDCl}_3+\text{D}_2\text{O}$ ), 6.42 (d, 2,  $J=0.5$  cps), 6.6-8.63 (c), 7.58 (s, 3), 8.99 (d, 3,  $J=6$  cps), 9.17 (s, 3).



### 15. Acetic Anhydride Cleavage of Dihydrodeoxycernuine

Dihydrodeoxycernuine (40mg) in acetic anhydride (4 ml) was heated at 100° for 20 hr, the excess anhydride hydrolyzed with dil  $\text{NH}_4\text{OH}$ , and the aqueous solution extracted with  $\text{CHCl}_3$ . The chloroform extracts were extracted with dil hydrochloric acid, the acidic extracts made basic with conc  $\text{NH}_4\text{OH}$  and extracted with  $\text{CHCl}_3$ . The residue obtained was chromatographed on alumina (0.35g, 5 ml fractions). Elution with ether -  $\text{CHCl}_3$  (1:1) gave product 28: 3mg; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 99.5:0.5) - homogeneous; ir ( $\text{CCl}_4$ )  $1625\text{ cm}^{-1}$ ; uv max (EtOH) 312  $\text{m}\mu$  ; uv max (EtOH,  $\text{H}^+$ ) 309  $\text{m}\mu$  ; mass spectrum m/e 332(14), 291(25), 290(100), 289(50), 275(33), 206(44), 192(35), 84(27).

### 16. Dihydrodeoxycernuine Monomethiodide(30)

Dihydrodeoxycernuine (60mg) was dissolved in ether (5 ml) and  $\text{CH}_3\text{I}$  (0.5 ml) was added. A gummy solid formed on the walls of the flask after a few minutes. After 6 hr the solvent was decanted. The residue crystallized on addition of acetone and was recrystallized from acetone containing a small amount of methanol yielding white crystals: mp 236-238°; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 85:15) - one component; nmr ( $\text{CDCl}_3$ )  $\tau$ 5.29 and 5.41 (two d showing further



fine structure, 2,  $\text{CH}-\text{N}^+$  protons), 5.77 and 5.89 (two m, 1), 6.44 (s, 3), 7.1-8.8 (c, 22), 9.01 (d, 3,  $J=6$  cps).

#### 17. $\text{NaBH}_4$ Cleavage of Dihydrodeoxycernuine Monomethiodide

The monomethiodide (55mg) was heated at reflux for 48 hr in ethanol (10 ml) containing  $\text{NaBH}_4$  (30mg). The reaction was worked up in the usual manner and the products purified by chromatography on alumina (2g, 20 ml fractions). The major and minor products, which eluted with ether -  $\text{CHCl}_3$  (19:1) were further purified by ptlc (0.75 mm alumina layers,  $\text{CHCl}_3$ ) then by evaporative distillation:

The major, less polar, product: 14mg; tlc -  $\text{Al}_2\text{O}_3(\text{CHCl}_3)$  - one component; ir ( $\text{CCl}_4$ ) 2785, 2710  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\tau$ 6.67-7.6 (series of broad m, 4-5,  $\text{CH}-\text{N}$  protons), 7.8 (s, 3), 7.8-9.0 (c), 9.11 (d, 3,  $J=6$  cps); mass spectrum m/e 264(11) 249(9), 220(5), 205(7), 192(7), 180(13), 166(13), 165(20), 152(100), 111(17), 110(29), 98(70).

The minor, more polar, product: tlc- $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 98:2) - one component; ir ( $\text{CCl}_4$ ) 2795 2740  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ , spectrum not calibrated) s ( $\text{CH}_3-\text{N}$ ), d ( $\text{CH}_3-\text{CH}$ ); mass spectrum m/e 264(14), 249(61), 220(3), 205(10), 192(6), 182(11), 167(16),







166(100), 164(17), 152(28), 138(30), 124(46), 112(31),  
111(29), 110(34), 98(55).

18. Cernuine Enamine (39)

Cernuine (38mg) was dissolved in 5% HOAc (8 ml) and mercuric acetate (180mg) was added. The reaction mixture was heated in an atmosphere of  $N_2$  on the steam bath for 42 hr with the addition of another 180mg of mercuric acetate after 14 and 28 hr. The precipitated mercurous acetate was filtered from the cooled solution, the filtrate saturated with  $H_2S$  and the resulting sulfides filtered off. The solution was then basified with  $NH_4OH$  and extracted with  $CH_2Cl_2$ . An evaporative distillation (bath temp  $120^\circ$ , 0.05 mm) of the residue obtained after drying ( $MgSO_4$ ), filtering and evaporating the solvent, provided the enamine (29mg, 72%) as a somewhat unstable colorless oil which solidified on standing: tlc -  $Al_2O_3$  ( $CHCl_3$ )-homogeneous; ir ( $CCl_4$ )  $1650\text{ cm}^{-1}$ ; uv max (EtOH) 235(sh), 215 m $\mu$ ; nmr ( $CCl_4$ )  $\tau$ 4.35 (d, 1,  $J=10$  cps, both members broadened by additional coupling,  $N-\underline{CH}-N$ ), 5.75-6.01 (c, 2,  $N-\underline{CH}-\underline{CH}=C-$ ), 6.74 (m, 1,  $\underline{CH}-N$ ), 7.5-7.75 (c, 2-3), 7.9-9.0 (c), 9.08 (d, 3,  $J=5.5$  cps); mass spectrum m/e 260 ( $C_{16}H_{24}N_2O$ , 35), 245(21), 231(14), 218(10), 217(21), 203(10), 190(13), 189(28), 163(28), 162(18),



149(16), 148(100), 120(12), 105(10).

The immonium perchlorate of the enamine 39 was prepared by addition of 70% perchloric acid-ethanol (1:1) to a solution of the enamine in ether. Recrystallization of the resulting precipitate from acetone-ether gave crystals: mp 174-175°; ir (Nujol) 1680, 1650  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O} \cdot \text{HClO}_4$ : C, 53.25; H, 6.98; N, 7.77. Found: C, 53.42; H, 6.98; N, 7.77.

#### 19. Hydrogenation of Cernuine Enamine

The enamine (30mg) was hydrogenated at atmospheric pressure in  $\text{CH}_3\text{OH}$  (15 ml) over 5% Pd/C (20mg) for 26 hr. The residue, obtained after removal of the catalyst and solvent and purification by evaporative distillation (110°, 0.05 mm), was identical (ir, tlc) with cernuine.

Hydrogenation of the immonium perchlorate under similar conditions also gave cernuine.

#### 20. $\text{NaBD}_4$ Reduction of Cernuine Enamine

Sodium borohydride- $\text{d}_4$  (15 mg) was added to a solution of the enamine (30mg) in  $\text{CH}_3\text{OH}$  (10 ml), and the resulting mixture was stirred for 17 hr at room temperature. The reaction mixture was worked up in the usual manner yielding 30mg of material which



crystallized slowly after an evaporative distillation: mp 83-85°; tlc -  $\text{Al}_2\text{O}_3(\text{CHCl}_3)$  - one major component; nmr ( $\text{CCl}_4$ )  $\tau$ 4.53 (q,  $J=13$  and 3 cps,  $\text{N}-\underline{\text{CH}}-\text{N}$ ), 6.5 (m, 1,  $\underline{\text{CH}}-\text{N}$ ), 7.18 (m, 1,  $\underline{\text{CH}}-\text{N}$ ), 7.64 (c, 2,  $\underline{\text{CH}}_2-\text{CO}-$ ), 7.9-9.0 (c), 9.12 (d, 3,  $J=6$  cps,  $\underline{\text{CH}}_3-\text{CH}$ ); mass spectrum  $m/e$  264(7), 263(40), 262(18), 248(13), 235(25), 234(100), 233(13), 221(45), 220(91), 207(11), 206(18), 192(17), 179(12), 164(16), 152(21), 151(16).

## 21. Acetylation of Cernuine Enamine

The enamine (150mg) was dissolved in 3 ml of acetic anhydride-pyridine (1:2) and left at room temperature for 23 hr. Work-up in the usual manner gave 130mg of material which consisted of two main products. Preparative tlc (silica gel layers,  $\text{CHCl}_3-\text{CH}_3\text{OH}$ , 93:7) yielded the less polar (higher  $R_f$  value) component in pure form: 28mg; ir ( $\text{CCl}_4$ ) 1645 (lactam  $\text{C}=\text{O}$ ), 1570-1530 (broad)  $\text{cm}^{-1}$ ; uv max (EtOH) 325  $m\mu$  ( $\epsilon$ 1200); nmr ( $\text{CDCl}_3$ )  $\tau$ 4.36 (d with further fine coupling, 1,  $J=8$  cps,  $\text{N}-\underline{\text{CH}}-\text{N}$ ), 5.46 (q, 1,  $J=10$  and 3 cps,  $\underline{\text{CH}}-\text{N}-\text{CO}$ ), 6.40-6.90 (c, 2), 7.5-8.0 (c, 3), 7.84 (c, 3,  $\underline{\text{CH}}_3-\text{CO}$ ), 8.0-8.9 (c), 9.05 (d, 3,  $J=6.5$  cps,  $\underline{\text{CH}}_3-\text{CH}$ ); mass spectrum  $m/e$  302(52), 287(72), 260(59), 259(100), 245(34), 243(24), 231(55), 217(33), 204(27), 203(19), 190(86).



## 22. Hydrogenation of the Acetylated Enamine

Hydrogenation of the acetylated enamine (6mg) was carried out in methanol (5 ml) containing 15mg of 5% Pd/C, at atmospheric pressure and room temperature for 13 hr. Filtration, evaporation of the filtrate, followed by an evaporative distillation gave a single product: tlc -  $\text{Al}_2\text{O}_3(\text{CHCl}_3)$ ; ir ( $\text{CHCl}_3$ )  $1650\text{ cm}^{-1}$ ; mass spectrum m/e 304(10), 275(37), 262(25), 261(100), 233(34), 219(12), 164(12), 151(14), 150(12), 149(22), 136(10), 134(56), 98(17), 97(12), 96(10).

## 23. Isolation of the Minor Alkaloids of L. Cernuum

A total of approximately 34g of basic extract (11.5g from 4l kg of dried plant material and a further 24g of extract from S.K.F.) yielded approximately 0.5g of alkaloidal material of higher  $R_f$  value (less polar) than cernuine and approximately 4g of minor alkaloidal material of lower  $R_f$  value than cernuine. As was mentioned in the discussion, the various minor alkaloids were isolated by repeated column and/or by repeated preparative thin layer chromatography on alumina.

Bases A: 3.5mg; an evaporative distillation (130-180°, 0.05 mm) yielded an oil; tlc -  $\text{Al}_2\text{O}_3$







(benzene-ether, 1:3) - two components in the ratio 7:3; ir ( $\text{CCl}_4$ ) 1755 (strong), 1730 (weak), 1680 (weak), 1630 (medium)  $\text{cm}^{-1}$ ; mass spectrum m/e 217(1), 211(1), 204(2), 203(9), 202(3), 196(3), 188(2), 183(3), 180(13), 172(8), 167(12), 165(11), 152(16), 147(21), 137(17), 124(15), 123(11), 121(12), 119(14), 111(100), 110(28), 109(55), 95(21), 93(13), 91(14), 86(10), 84(19), 81(18), 79(17), 77(17), 69(20), 67(41).

Base B: 2mg; an evaporative distillation (130-180°, 0.05 mm) yielded a colorless solid; tlc -  $\text{Al}_2\text{O}_3$  (ether) - one major component; ir ( $\text{CCl}_4$ ) 2860, 2790, 2730, 1450  $\text{cm}^{-1}$ ; mass spectrum m/e 248(20), 247(39), 233(9), 220(20), 219(100), 206(23), 205(40), 191(10), 177(8), 164(10), 151(10), 150(13), 137(9), 110(7), 84(15).

Base C: 15mg; dihydrodeoxycernuine.

Base D: 2mg; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ ) - one major component with a trace of cernuine; ir ( $\text{CCl}_4$ ) 3630, 3300, 1565, 1545  $\text{cm}^{-1}$ ; mass spectrum m/e 262(3), 258(3), 233(8), 220(8), 219(5), 205(9), 149(7), 146(6), 144(6), 130(11), 117(6), 112(5), 99(19), 98(100), 70(26), 57(16), 55(15).

Base E: 12mg; an evaporative distillation (180-200°, 0.05 mm) yielded a yellow solid; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CH}_2\text{Cl}_2$ - $\text{CHCl}_3$ , 1:1) - one component; ir ( $\text{CCl}_4$ )



3080-3020, 2850, 2790, 1720 (medium), 1600 (medium), 1500 (strong)  $\text{cm}^{-1}$ ; uv max (EtOH) 270, 229 (sh), 210  $\text{m}\mu$ ; uv max (EtOH,  $\text{H}^+$ ) 270, 231 (sh), 210  $\text{m}\mu$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 1.7 (d with further fine coupling, 1,  $J=8$  cps), 3.5 (m, 1), 6.2 (s, 3), 6.4 (s, 3), 6.8-7.1 (c, 4-5), 7.2-7.8 (c, 2-3), 7.5 (s, 3), 8.1-9.0 (c), 8.8 (s, 3); mass spectrum m/e 296(17), 295( $\text{C}_{19}\text{H}_{21}\text{NO}_2$ , 91), 294(100), 280( $\text{C}_{18}\text{H}_{18}\text{NO}_2$ , 38), 264( $\text{C}_{18}\text{H}_{18}\text{NO}$ , 31), 252( $\text{C}_{17}\text{H}_{16}\text{O}_2$ , 20), 237(11), 221( $\text{C}_{16}\text{H}_{13}\text{O}$ , 23).

Base F: 8mg; an evaporative distillation ( $150^\circ$ , 0.02 mm) yielded an oil which crystallized; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CH}_2\text{Cl}_2$ - $\text{CHCl}_3$ , 1:1) - one component; ir ( $\text{CCl}_4$ ) 3090-3010, 2930, 2850, 2800, 2765, 1600 (weak)  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 2.5-3.0 (c), 7.5-7.8 (c), 7.7 (s), 8.3-8.9 (c), 8.8 (s); mass spectrum m/e 309( $\text{C}_{21}\text{H}_{27}\text{NO}$ , 2), 232( $\text{C}_{15}\text{H}_{22}\text{NO}$ , 2), 127(4), 111(2), 105(5), 99(8), 98( $\text{C}_6\text{H}_{12}\text{N}$ , 100).

Base G: 23mg; an evaporative distillation ( $180^\circ$ , 0.02 mm) yielded a partly crystalline oil; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 97:3) - homogeneous except for a trace of polar impurity; ir ( $\text{CHCl}_3$ ) 3590, 3520, 3440, 3400, 1750, 1680, 1660, 1460  $\text{cm}^{-1}$ ; uv max (EtOH) 217  $\text{m}\mu$ ; mass spectrum m/e 264(2), 185(13), 153(18), 152(100), 150(10), 111(14), 110(23), 81(12).



Base H: 30mg; obtained from chromatographic fractions containing traces of lycocernuine by removal of the lycocernuine (crystallization from acetone-ether) followed by evaporation of the mother liquors; recrystallization from acetone-ether gave crystals (dried under vacuum at the reflux temperature of benzene) of mp 145-147°; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 98:2), tlc -  $\text{SiO}_2$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 9:1) - homogeneous; ir ( $\text{CHCl}_3$ ) 3610, 3470, 3440, 2850, 2800, 2750, 1715  $\text{cm}^{-1}$ ; nmr (acetone- $\text{d}_6$ )  $\tau$ 2.25-3.3 (c, 6-7), 5.9 (m, 2), 6.46 (s, 3), 6.4-7.6 (c), 7.6-8.8 (c); mass spectrum m/e 354 ( $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3$ , 95), 253(100), 184(10), 170(12), 169(14), 156(8).

Acetylation of Base H was carried for 20 hr: tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CH}_2\text{Cl}_2$ - $\text{CHCl}_3$ , 1:1) - homogeneous; ir ( $\text{CCl}_4$ ) 3475, 2850, 2790, 2740, 1740, 1720, 1230  $\text{cm}^{-1}$ ; mass spectrum m/e 396 ( $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_4$ , 5), 395(4), 336(55), 335(48), 278 ( $\text{C}_{19}\text{H}_{22}\text{N}_2$ , 100), 277 ( $\text{C}_{19}\text{H}_{21}\text{N}_2$ , 93), 184(44), 169(27), 156(45).

Base I: 15mg; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 93:7) - one major component ; ir ( $\text{CHCl}_3$ ) 3590, 3400 (broad), 1710(sh), 1660-1620, 1460  $\text{cm}^{-1}$ ; mass spectrum m/e 278 ( $\text{C}_{17}\text{H}_{30}\text{N}_2\text{O}$ , 11), 261(13), 249(18), 219(39), 152(67), 136(42), 110(33), 98 ( $\text{C}_6\text{H}_{12}\text{N}$ , 100), 95(38), 93(33), 71(41), 69(58).



Acetylation of Base I was carried out under the usual conditions for 13 hr. The product was a mixture of two components (tlc) which were not separable by column chromatography over alumina: ir ( $\text{CCl}_4$ ) 1740, 1660, 1650(weak)  $\text{cm}^{-1}$ ; mass spectrum m/e 320(5), 277(8), 261(25), 260(11), 259(8), 245(17), 220(11), 219(35), 164(15), 163(14), 162(11), 150(34), 149(33), 136(18), 134(14), 121(16), 111(16), 109(26), 108(20), 107(19), 98(100), 95(28), 93(22), 83(33), 82(34), 81(30).

Base J: 20mg; an evaporative distillation (130-180°, 0.05 mm) yielded a glassy solid; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 95:5) - homogeneous except for a trace of less polar impurity; ir ( $\text{CHCl}_3$ ) 3680, 3600, 3400 (broad), 1680  $\text{cm}^{-1}$ ; mass spectrum m/e 264(23), 246(65), 220(30), 219(45), 206(36), 205(42), 166(31), 150(27), 136(26), 98(100), 83(51).

Acetylation of Base J was carried out under the usual conditions for 48 hr. Chromatography of the product on alumina yielded a monoacetyl derivative: tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ ) - homogeneous; ir ( $\text{CCl}_4$ ) 1735, 1695  $\text{cm}^{-1}$ ; mass spectrum m/e 306(10), 263(76), 246(100), 245(36), 219(20), 163(25), 149(22), 121(25), 81(29), 69(29), 55(46).







Reduction of Base J was attempted with  $\text{NaBH}_4$  in  $\text{CH}_3\text{OH}$  at room temperature for 24 hr. Starting material was recovered.

Reduction of Base J with excess  $\text{LiAlH}_4$  in ether for 24 hr followed by the usual work-up yielded a less polar material which was purified by chromatography on alumina: tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 97:3) - homogeneous; ir ( $\text{CHCl}_3$ ) 3330 (broad)  $\text{cm}^{-1}$ .

Base K: 48mg; purified by an evaporative distillation ( $170^\circ$ , 0.03 mm); tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 94:6) - homogeneous; ir ( $\text{CHCl}_3$ ) 3370, 1670  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\tau$ 2.74 (d, 1,  $J=2$  cps), 4.2 (broad s, 2,  $W/2=15$  cps), 5.3-7.8 (c, 8), 7.9-8.9 (c, 18-22), 9.05 (d, 3,  $J=5$  cps); mass spectrum m/e 278 ( $\text{C}_{17}\text{H}_{30}\text{N}_2\text{O}$ , 15), 249(11), 221(19), 185(11), 166 ( $\text{C}_{11}\text{H}_{20}\text{N}$ , 62), 152 ( $\text{C}_{10}\text{H}_{18}\text{N}$ , 100), 150(24), 112(69), 56(25).

Reduction of Base K with excess  $\text{LiAlH}_4$  was carried out in refluxing ether for 12 hr. Work-up in the usual manner yielded a product which was purified by chromatography on alumina: tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 95:5) - one major component with a few trace impurities; ir ( $\text{CCl}_4$ ) 2850, 2780, 2700, 1450  $\text{cm}^{-1}$ ; mass spectrum m/e 264 ( $\text{C}_{17}\text{H}_{32}\text{N}$ , 1.5), 150 ( $\text{C}_{10}\text{H}_{16}\text{N}$ , 6), 98 ( $\text{C}_6\text{H}_{12}\text{N}$ , 100).



Hydrolysis of Base K was carried out in refluxing ethanol-water (1:1) containing 10% KOH for 12 hr.

Work-up yielded one major product which was purified by ptlc on alumina: tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 8:2) - homogeneous; mass spectrum m/e 250(10), 185(7), 166(14), 163(10), 150(37), 97(33), 84( $\text{C}_5\text{H}_{10}\text{N}$ , 100).

Base L: 5mg; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 99:1) - one component; ir ( $\text{CCl}_4$ ) 1680, 1645, 1270  $\text{cm}^{-1}$ ; uv max (EtOH) 213 m $\mu$  ; mass spectrum m/e 262(100), 233(98), 220(94), 219(50), 152(24), 98(30).

Base M: 4mg of acetylated alkaloid; tlc -  $\text{SiO}_2$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 93:7) - one component; ir ( $\text{CCl}_4$ ) 1730 (medium), 1670 (strong), 1640 (strong), 1430, 1260  $\text{cm}^{-1}$ ; mass spectrum m/e 320(10), 291(14), 276(14), 209(20), 208(100), 112(73), 84(80).



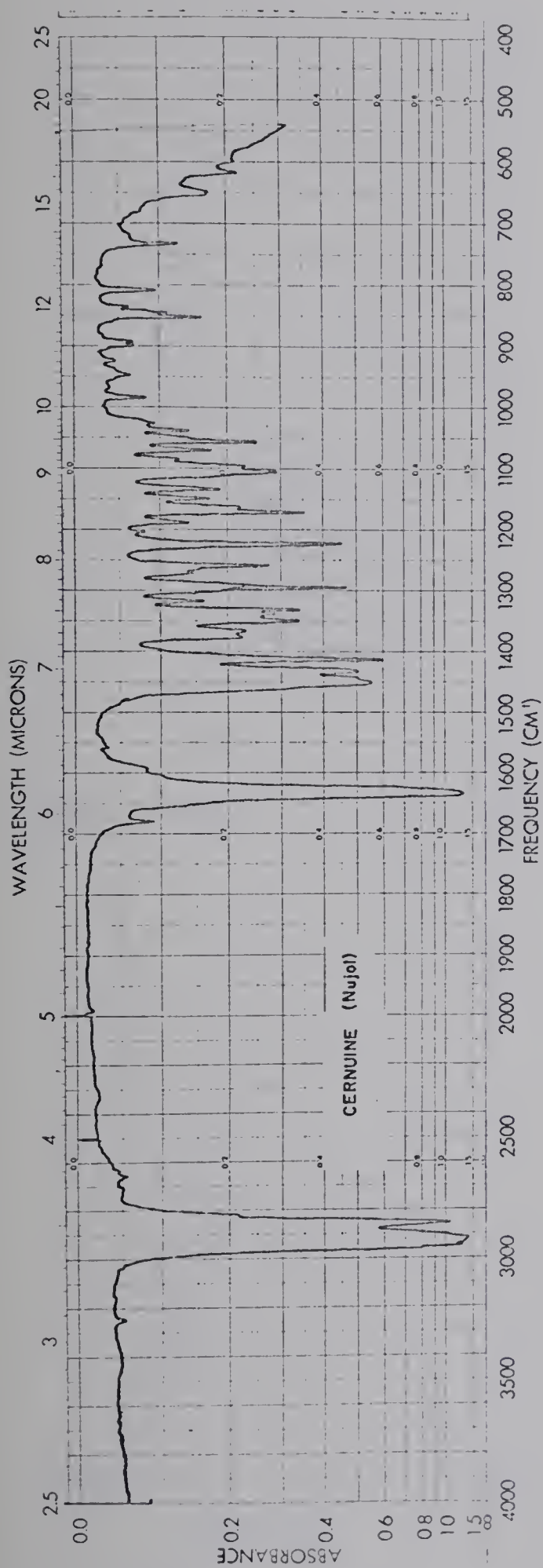


FIGURE 1

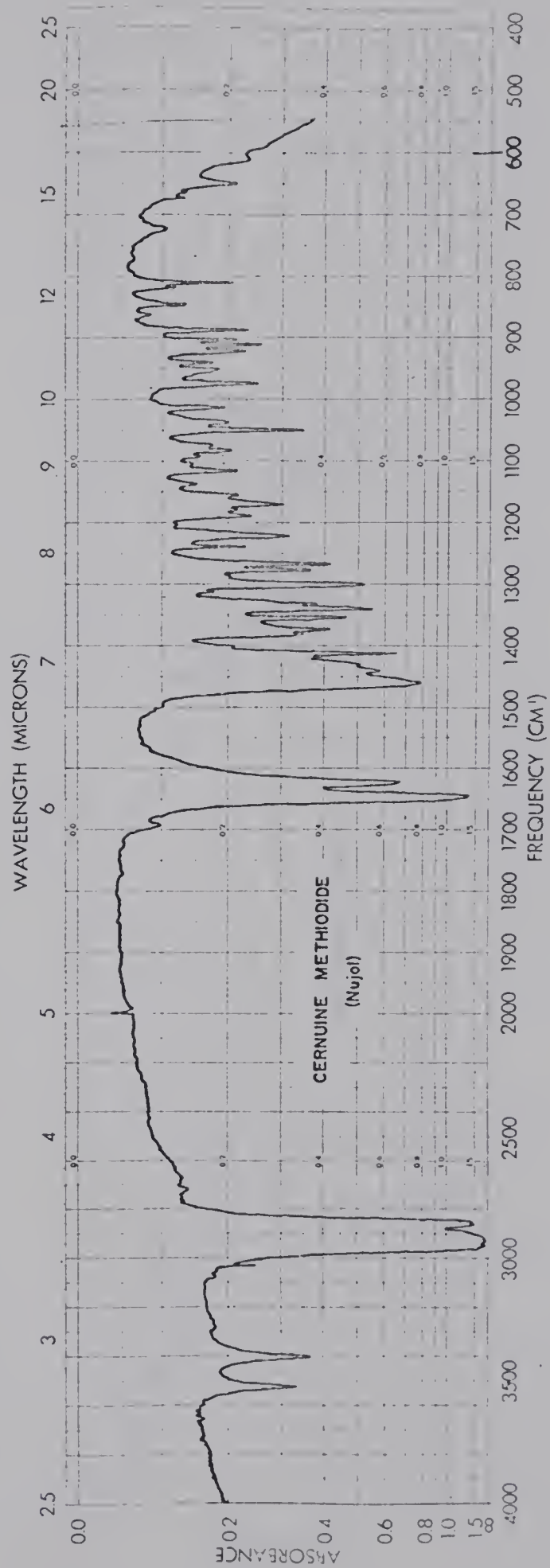


FIGURE 2





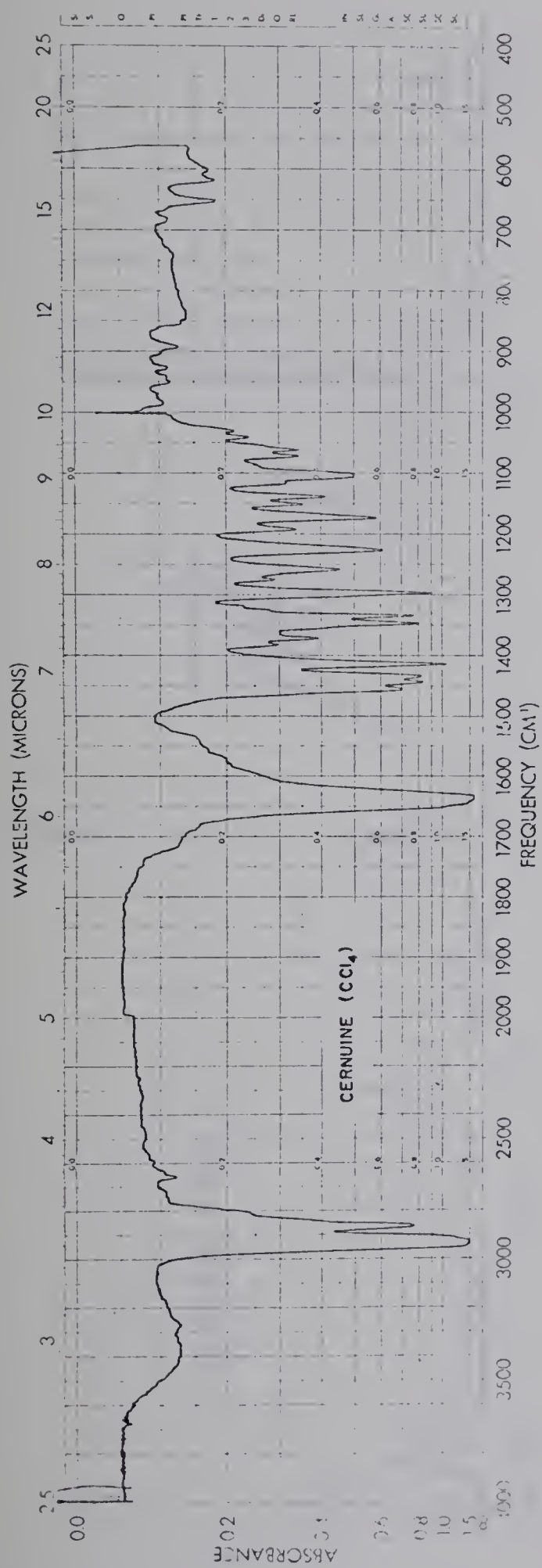


FIGURE 3

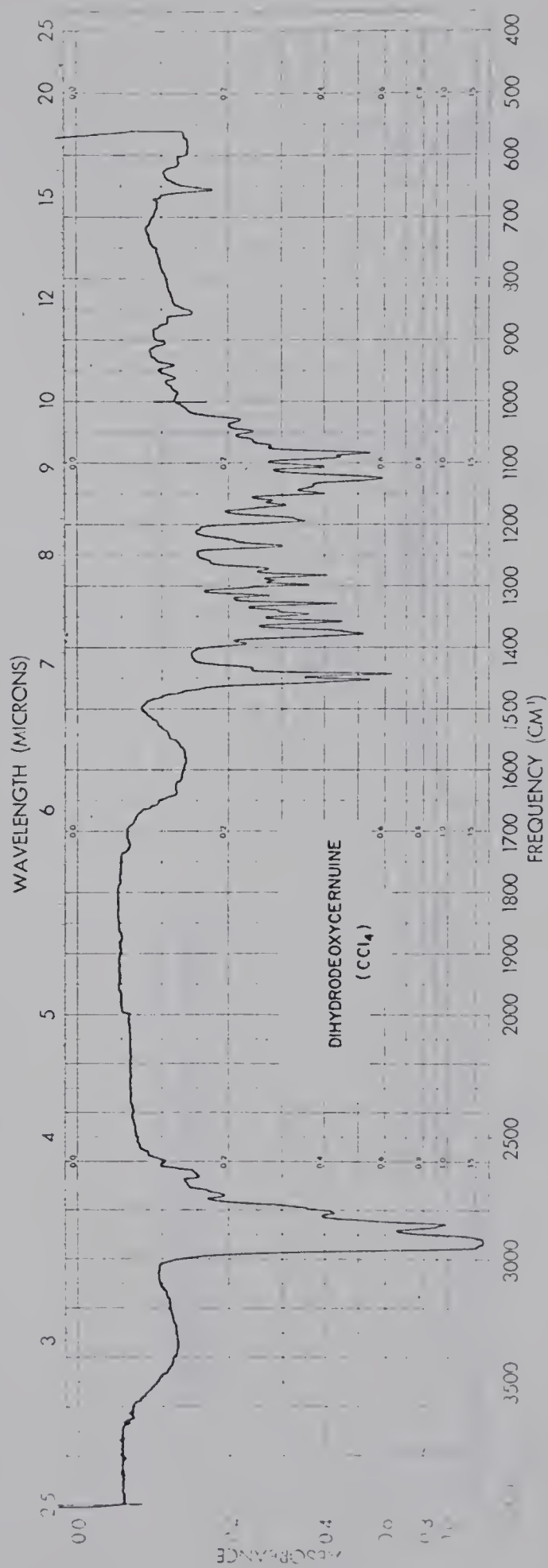


FIGURE 4





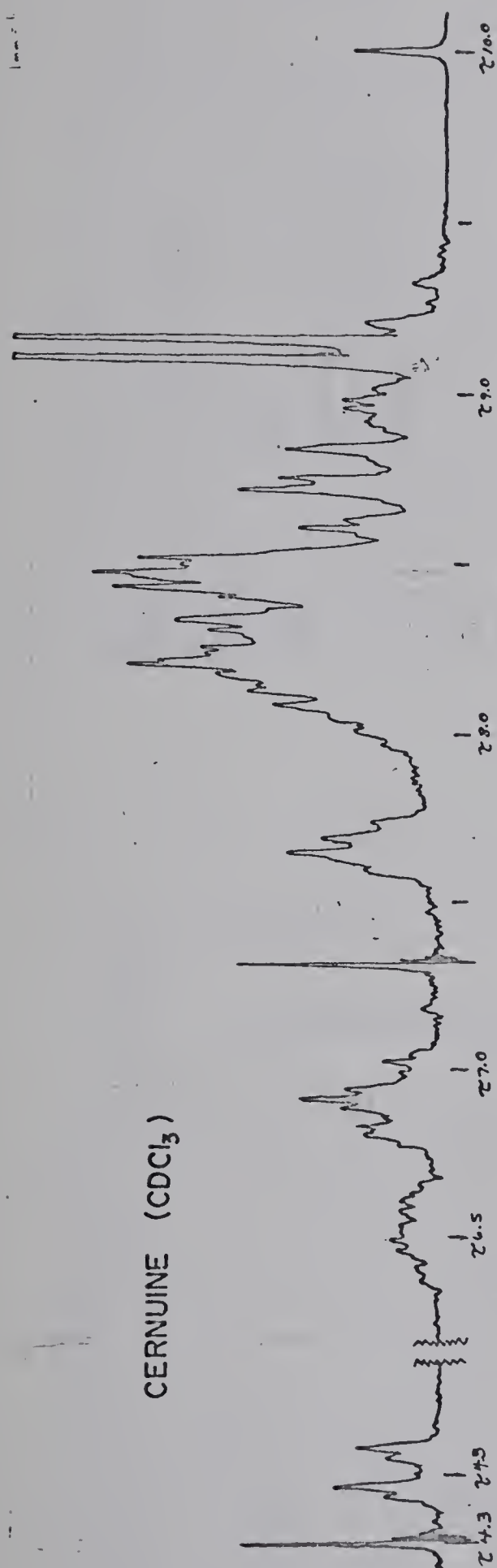


FIGURE 5

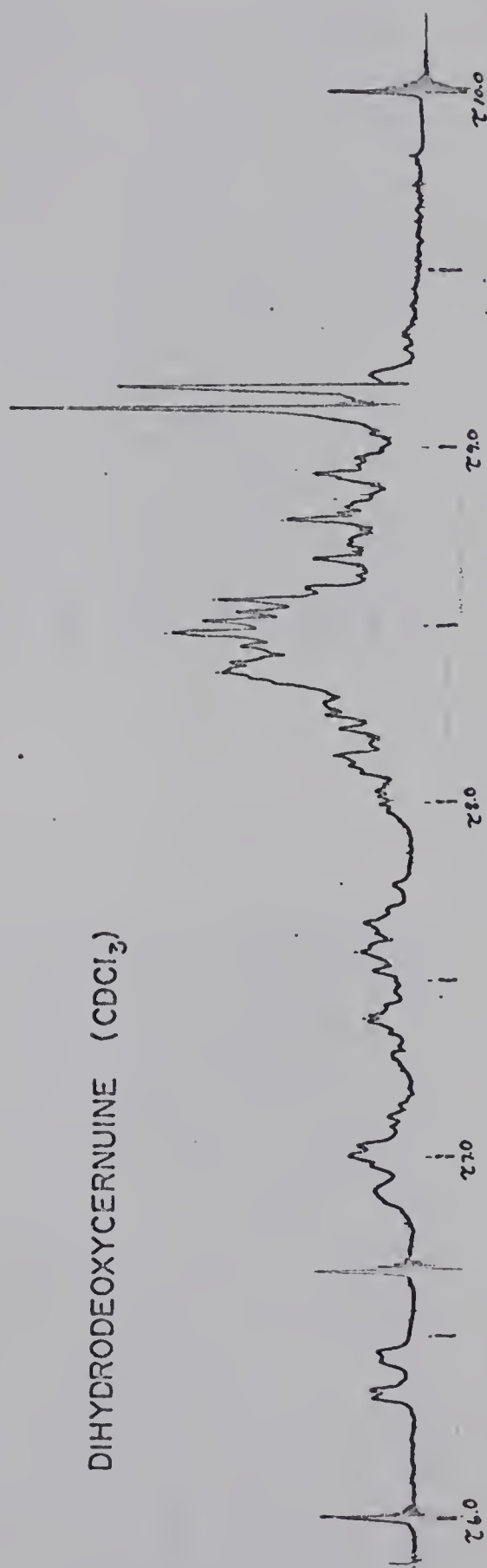


FIGURE 6



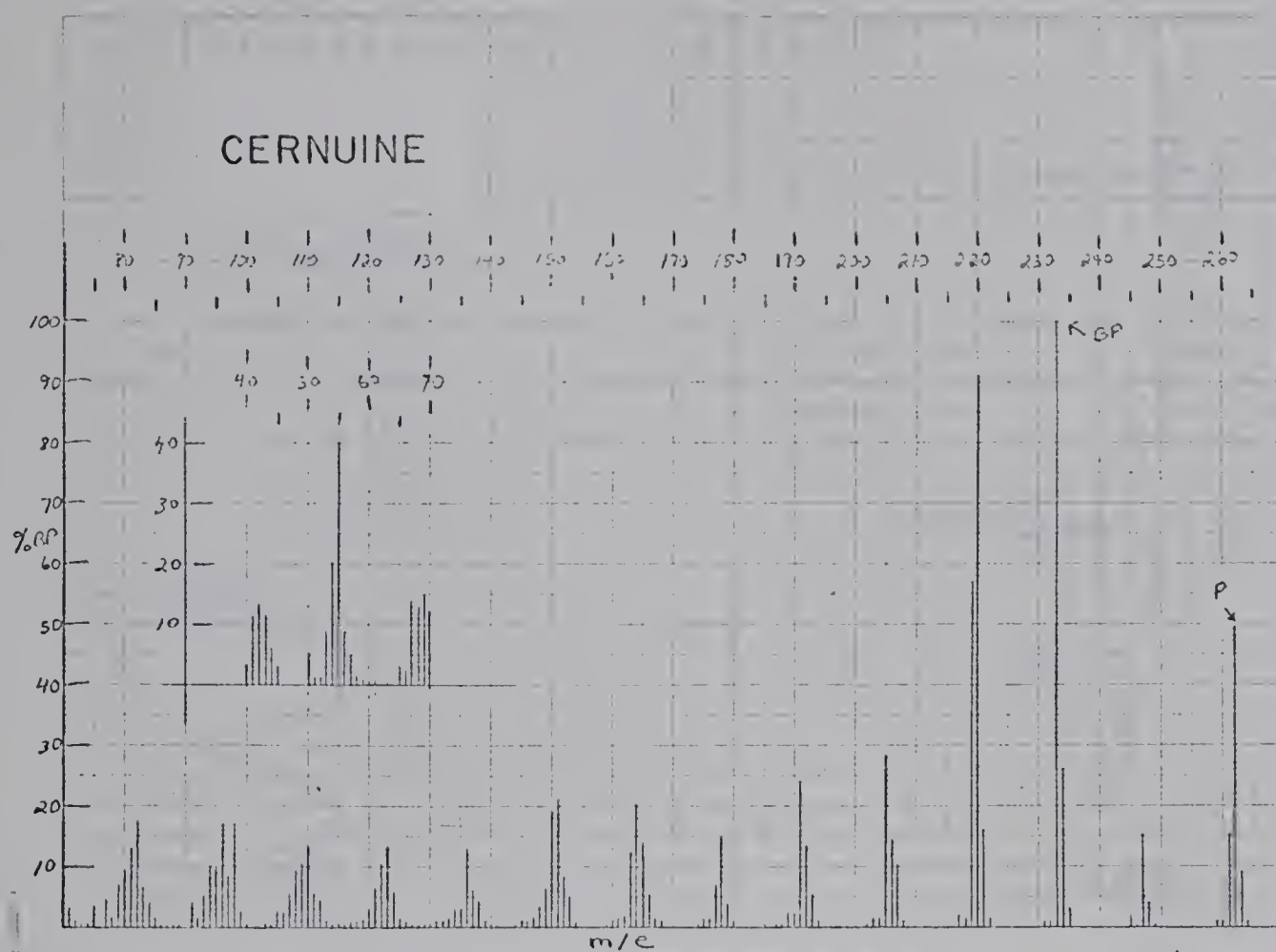


FIGURE 7

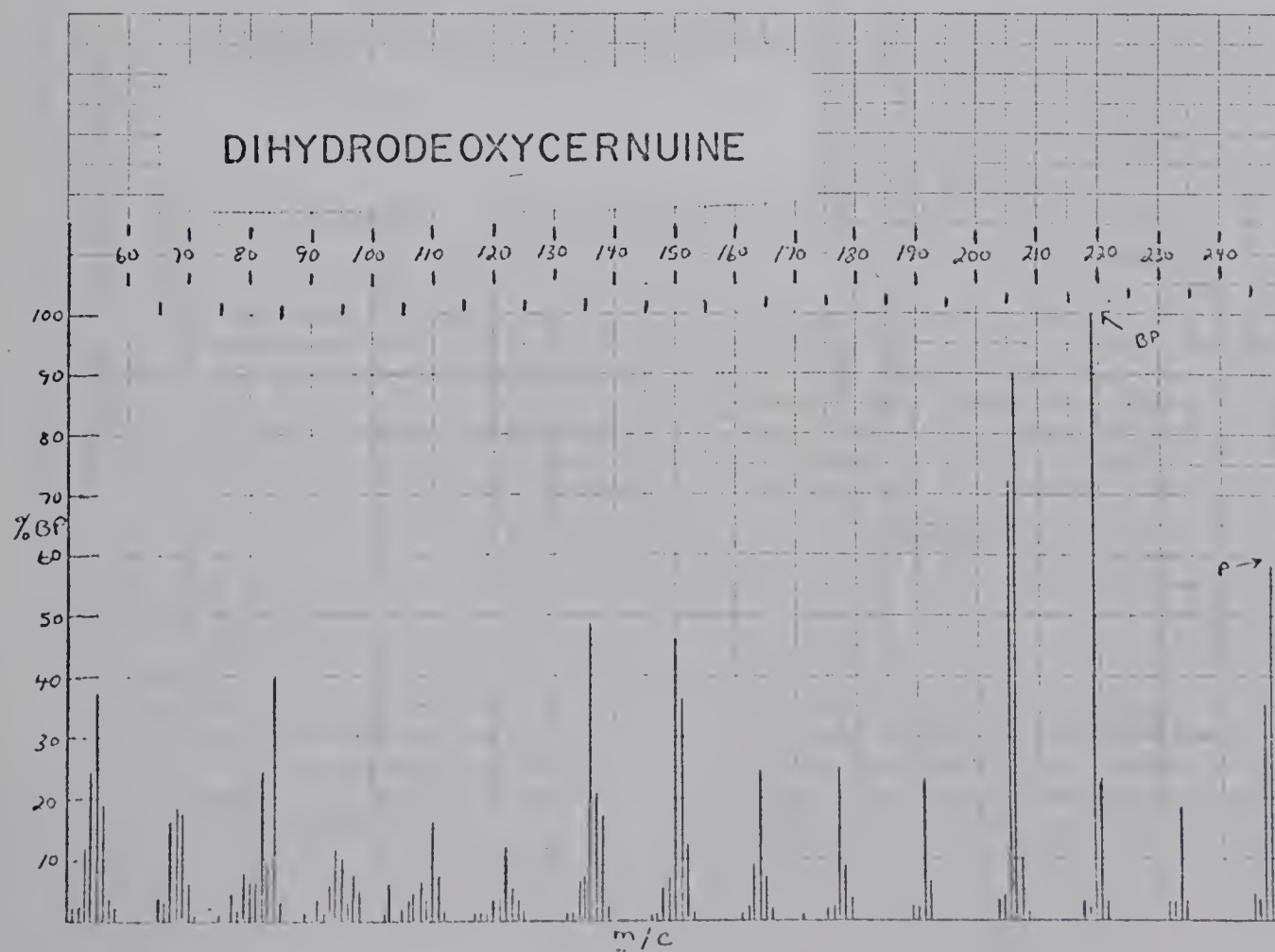


FIGURE 8



2-n-BUTYL-4-METHYL-6-n-PENTYL-  
PYRIDINE (Dehydrog. prod.)

(CDCl<sub>3</sub>)

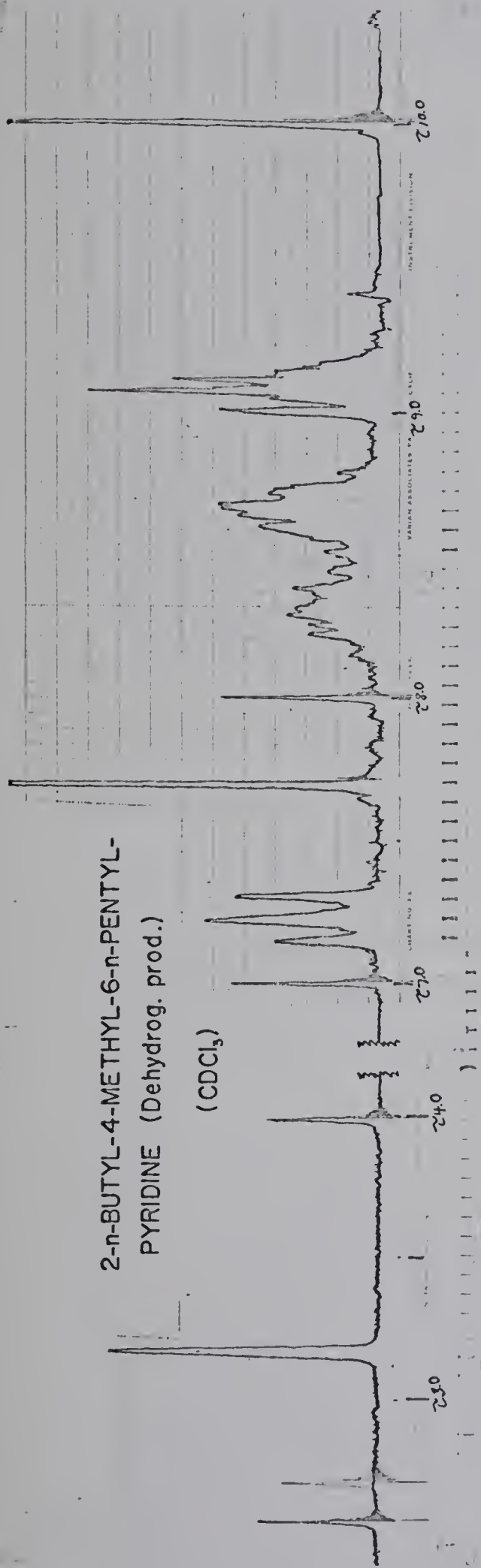


FIGURE 9

2-n-BUTYL-4-METHYL-6-n-PENTYL-  
PYRIDINE (Synthetic prod.)

(CDCl<sub>3</sub>)

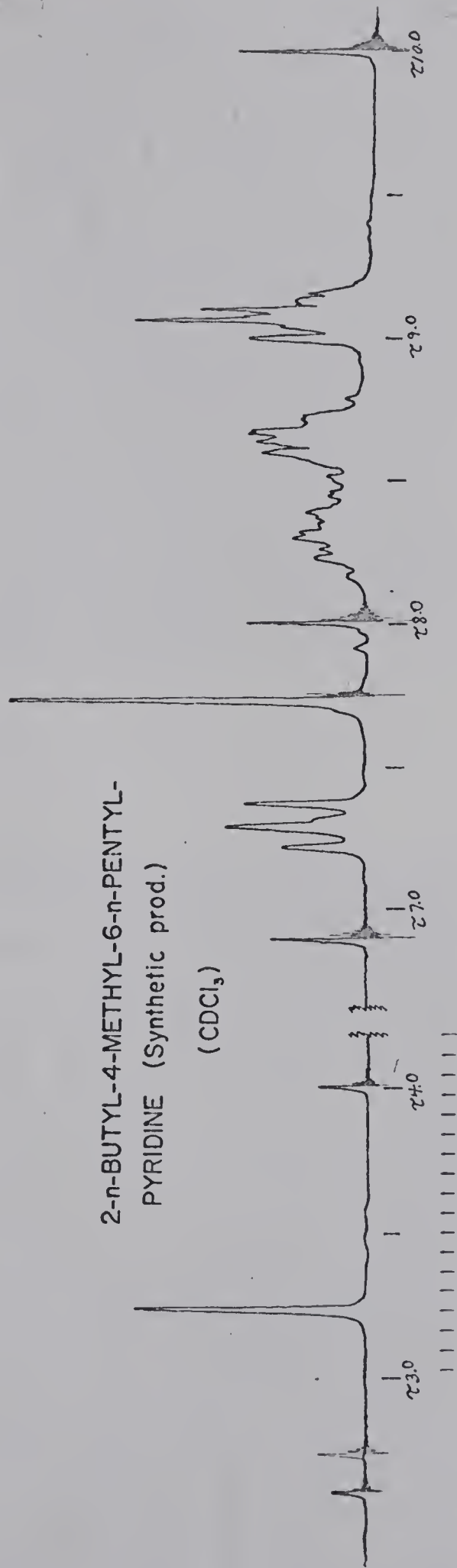


FIGURE 10



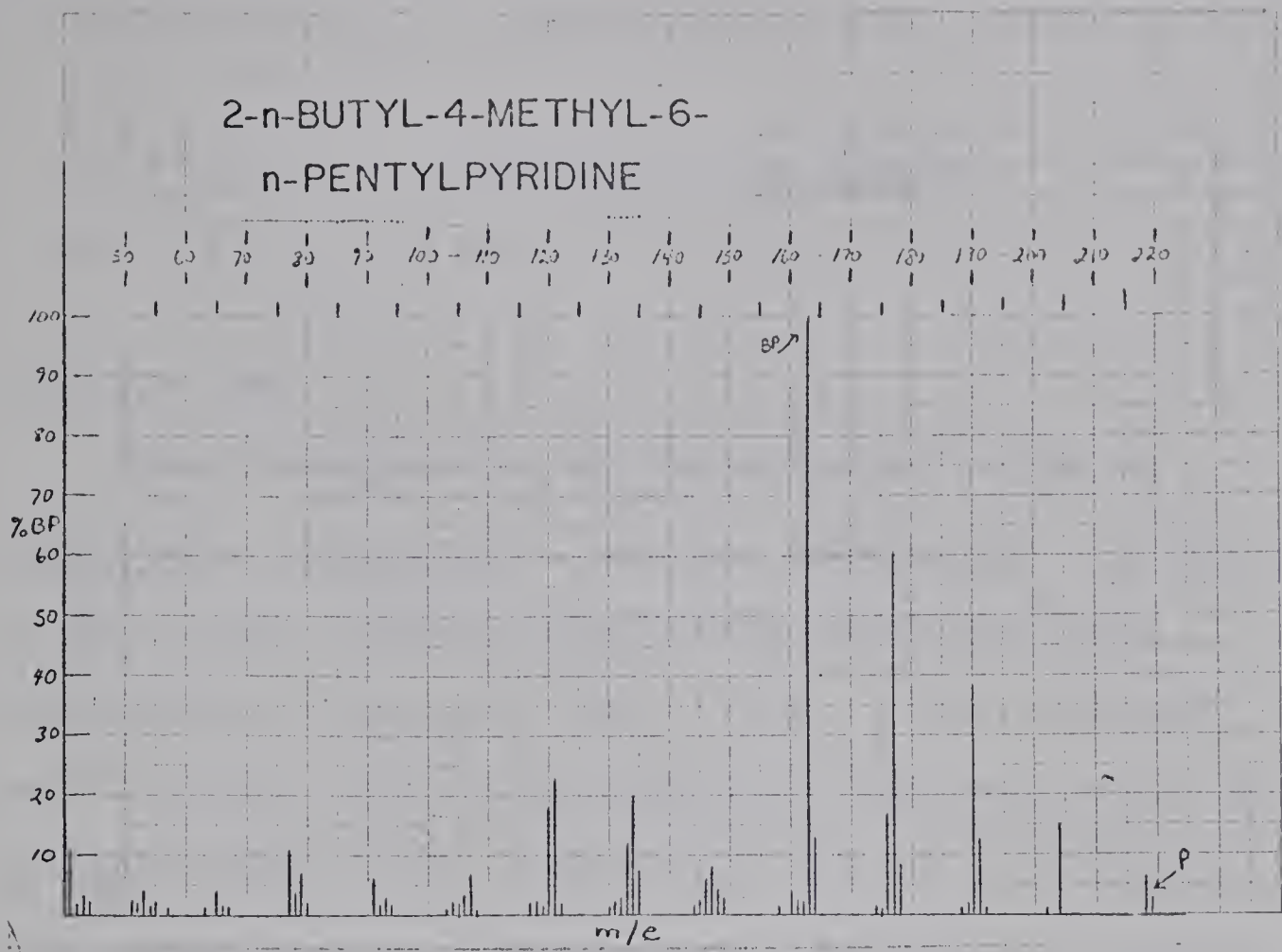


FIGURE 11

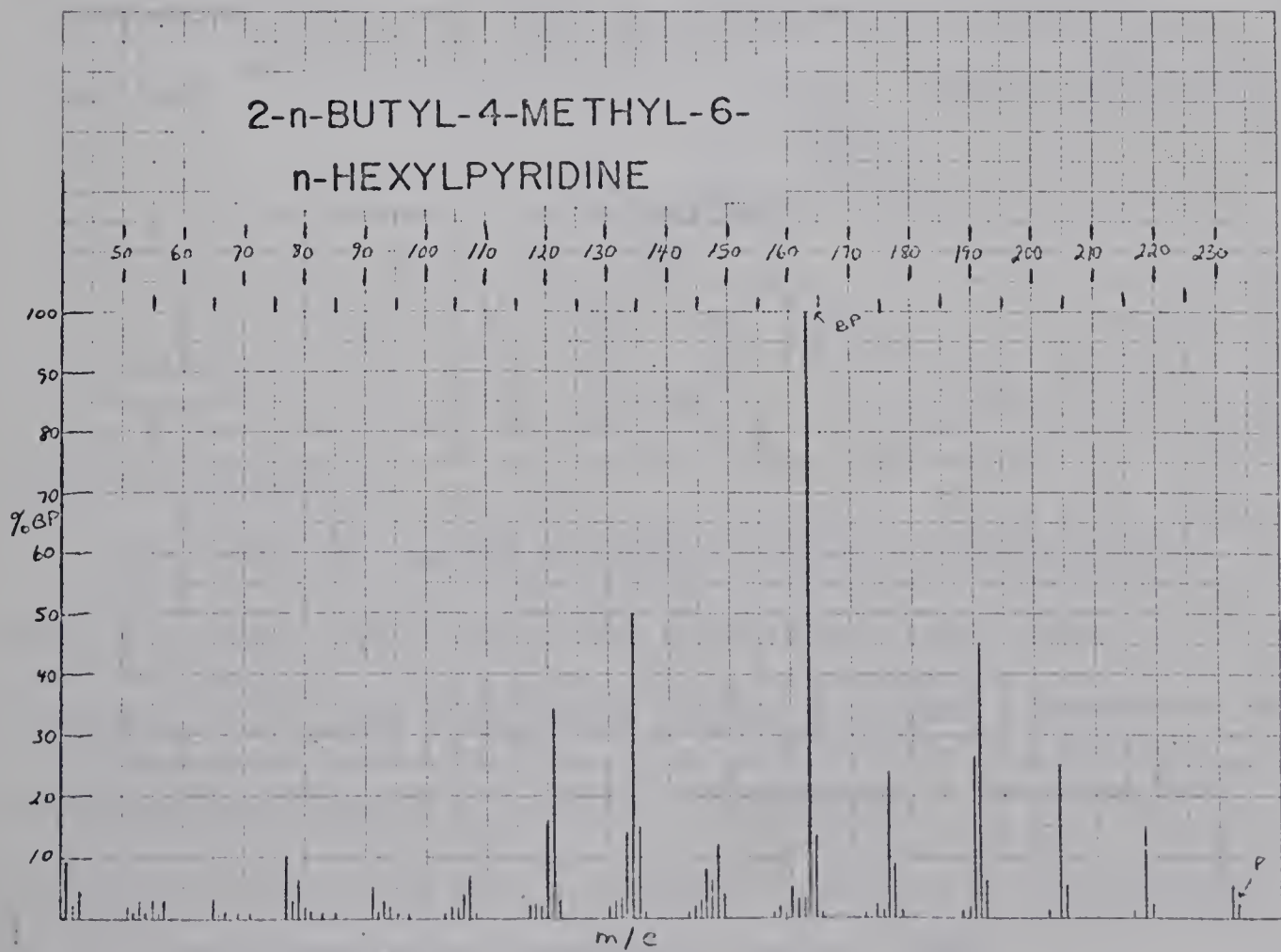


FIGURE 12

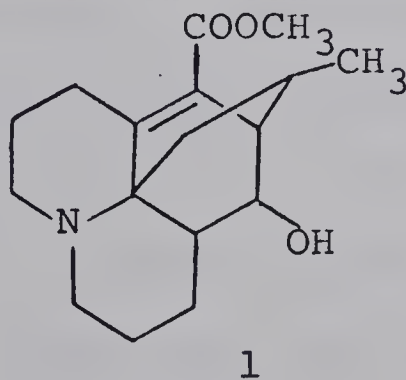




## DISCUSSION AND RESULTS

## SECTION TWO

The investigation of the minor alkaloids of Lycopodium annotinum L. in this laboratory\* yielded a previously unreported alkaloid which was named annopodine,  $C_{17}H_{25}NO_3$  (mol wt 291). This alkaloid was isolated from chromatographic fractions which had yielded crystalline  $\alpha$ -obscurine and was purified by recrystallization from acetone. Preliminary investigations\*, which included a study of the spectral characteristics as well as some simple chemical transformations, as well as biogenetic reasoning, resulted in the tentative structure 1 being proposed



for annopodine.

Because of the very small supply of annopodine the further investigations described here were limited to a few reactions which yielded little information about the gross structure. In view of

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\* G.G. Iverach, Ph.D. Thesis, U. of A., 1963



these results, especially those from the dehydrogenation reactions, which were not readily interpretable on the basis of the tentative structure for annopodine, we set out to prepare a heavy atom derivative for X-ray diffraction studies. The degradative results, as well as the other physical and chemical properties of annopodine will be discussed in light of the structure of annopodine as determined by X-ray analysis\*.

Two heavy atom derivatives were prepared. The methiodide was prepared in methanol and recrystallized from acetone. Drying under vacuum at the reflux temperature of benzene resulted in fractures forming in the crystals, while at room temperature under vacuum colorless crystals more suitable for X-ray diffraction measurements were obtained. Preliminary studies indicated that these crystals were orthorhombic, space group  $P2_12_12_1$ , with  $a = 11.7$ ,  $b = 24.1$  and  $c = 8.24 \text{ \AA}$  (cell volume  $2320 \text{ \AA}^3$ ). The calculated density of  $1.242 \text{ g/cm}^3$  indicated that there were four molecules per unit cell. The experimentally determined value for the density of the methiodide using the neutral density method, gave a value of  $1.402 \pm 0.002 \text{ g/cm}^3$ . The difference was thought to be due to the incorporation

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\*Work done by N. Masaki, Post-doctoral Fellow, U. of A., 1967.



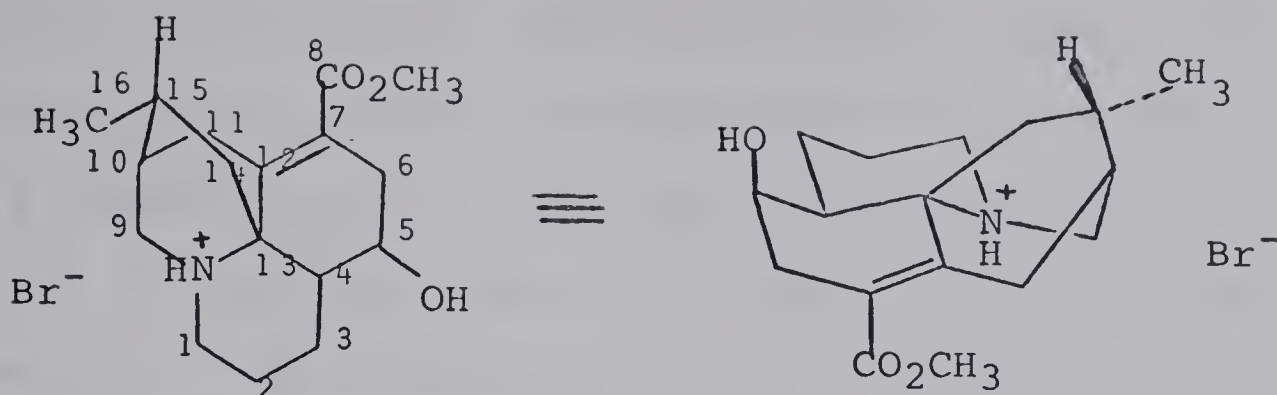
of solvent molecules in the crystal, and in fact this was shown to be the case. When a low temperature mass spectrum was recorded an intense peak at  $m/e$  58 indicated the presence of acetone. The calculated density, assuming one molecule of acetone per unit cell in addition to the four molecules of annopodine is  $1.410 \text{ g/cm}^3$  which compares favourably with the experimental value. The fact that a molecule of solvent is incorporated into the crystal and that the unit cell volume is larger than desirable made this derivative a poor choice for X-ray diffraction studies.

The hydrobromide of annopodine, prepared in methanol with anhydrous hydrogen bromide and recrystallized from ethyl acetate, formed more suitable crystals. These crystals were orthorhombic, space group  $P2_1^2 2_1^2 2_1^2$ , with  $a = 13.4$ ,  $b = 14.0$  and  $c = 9.0 \text{ \AA}$  (cell volume  $1685 \text{ \AA}^3$ ). The calculated density of  $1.465 \text{ g/cm}^3$  again indicated four molecules per unit cell and compared favourably with the experimental density of  $1.423 \pm 0.002 \text{ g/cm}^3$  indicating that no solvent molecules were incorporated into the crystal lattice.

The X-ray structural determination of annopodine was done on the hydrobromide and showed that it has the following structure.







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The bromide ion that is associated with the nitrogen of one molecule is believed to be hydrogen bonded to the hydroxyl group of another molecule.

The data\* obtained previous to this investigation is in complete accord with the structure of annopodine. The infrared spectrum (Nujol) of annopodine indicates the presence of the hydroxyl ( $3300\text{ cm}^{-1}$ ) and the ester conjugated to the double bond ( $1710$ ,  $1640$  and  $1225\text{ cm}^{-1}$ ). The absence of Bohlmann bands in the infrared is consistent with the structure. The maximum in the ultraviolet at  $225\text{ m}\mu$  ( $\log \epsilon = 3.8$ ) is typical of the  $\alpha, \beta$  - unsaturated ester<sup>87a</sup>. Annopodine should show in its nmr spectrum one low field signal for the hydrogen at C-5 and in fact this is observed as a multiplet at  $\tau 5.96$  (the multiplet shifts to  $\tau 4.84$  in the acetylated derivative). The value of  $W_{\frac{1}{2}}$  (9 cps) for the C-5 proton is in agreement with the fact that the hydroxyl group is

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\*G.G. Iverach, Ph.D. Thesis, U. of A., 1963.

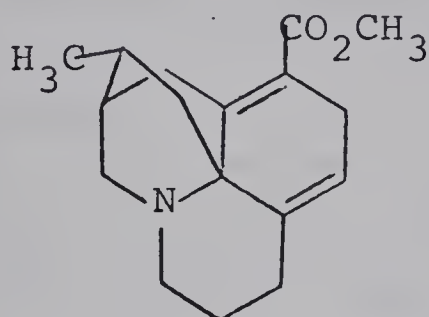




axially orientated<sup>120</sup>. The ester protons appear as a three proton singlet at  $\tau$ 6.28 and the C-15 methyl as a doublet at  $\tau$ 8.95 ( $J=6$  cps). The ketone obtained by the oxidation of annopodine shows in its infrared spectrum ( $\text{CCl}_4$ ) absorption at 1710 and 1698  $\text{cm}^{-1}$  and a maximum in its ultraviolet spectrum at 228  $\text{m}\mu$ . The value of 1698  $\text{cm}^{-1}$  for the ketone is in accord with the ketone being present in a six membered ring and indicates that it is not conjugated to the  $\alpha,\beta$ -unsaturated ester grouping. The fact that the ultraviolet maximum did not change appreciably also agrees with this view. The result of the acetylation experiment, which indicated that no N-acetyl group had been introduced, agrees with the fact that the nitrogen present in annopodine is tertiary. Dehydration of annopodine with phosphorous oxychloride - pyridine yielded anhydroannopodine. Absorption in the infrared at 1710 and 1640  $\text{cm}^{-1}$  and no strong absorption above 225  $\text{m}\mu$  in its ultraviolet spectrum indicated that the double bond introduced is not conjugated to the existing chromophore. In agreement with the infrared and ultraviolet spectra, the nmr spectrum showed an unresolved low field multiplet at  $\tau$ 4.52 which integrated for approximately one proton. Thus in light of the

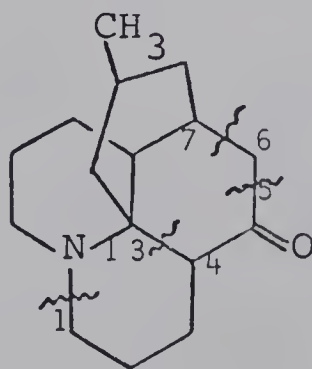


structure for annopodine, dehydration must have taken place between C-4 and C-5 and 54 must be the structure of anhydroannopodine.



54

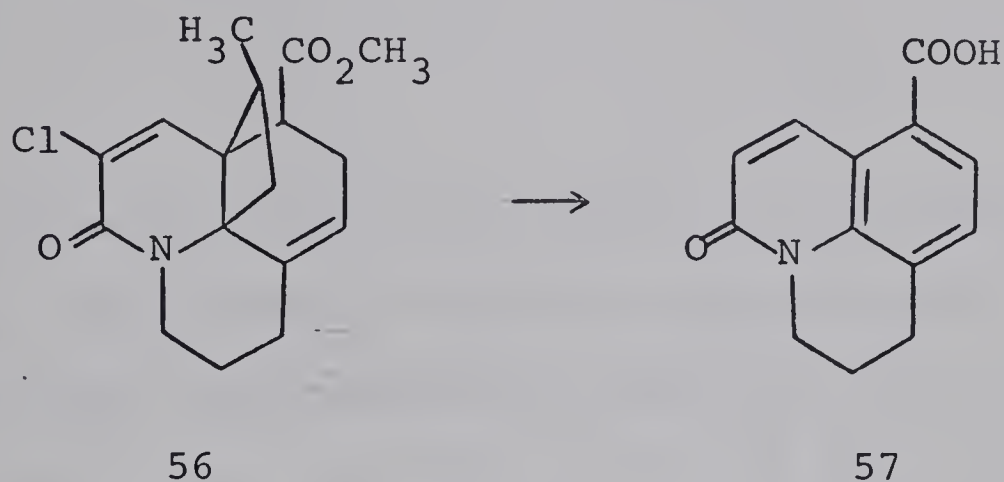
Dehydrogenation studies had been most informative in the determination of the structure of cernuine, therefore the major amount of annopodine available was committed to dehydrogenation in the hope of isolating a quinoline which would indicate the place of attachment of the bridge and perhaps the ester group. Dehydrogenation experiments on lycopodine by Marion and Manske<sup>90</sup> yielded 7-methylquinoline and 5,7-dimethylquinoline, presumably by cleavage of the N - C-1, C-4 - C-13, and C-6 - C-7 or C-5 - C-6 bonds as shown in 55.



55

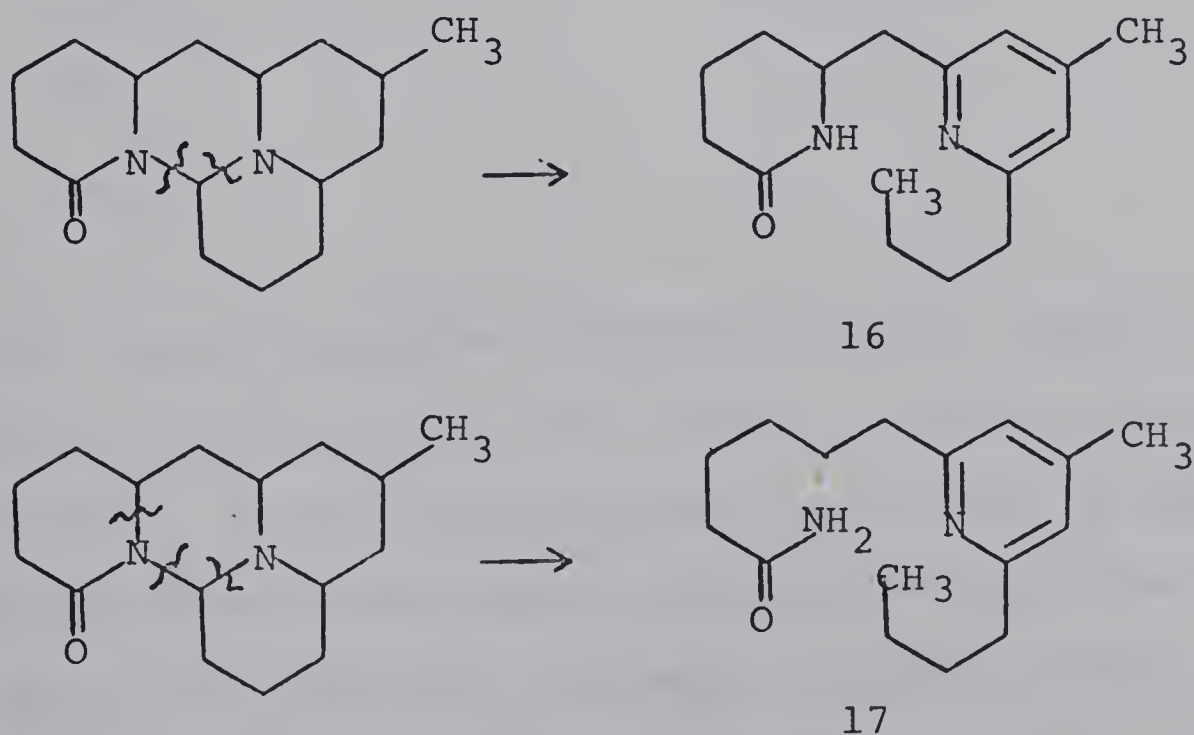


Wiesner, Valenta, Ayer and Bankiewicz<sup>91</sup> subjected the anhydro ester derivative 56, obtained from ananinine by a number of steps, to dehydrogenating conditions and isolated a quinolone acid 57.

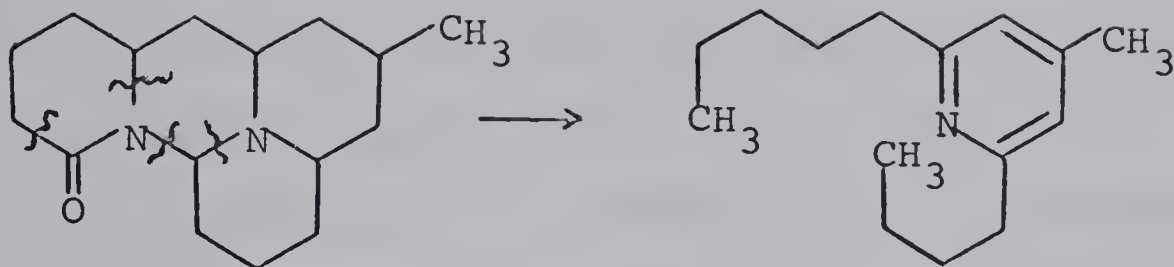


Cernuine, when subjected to dehydrogenating conditions, as mentioned in Section One, cleaved in the following ways and yielded the products as shown below.

SCHEME 16

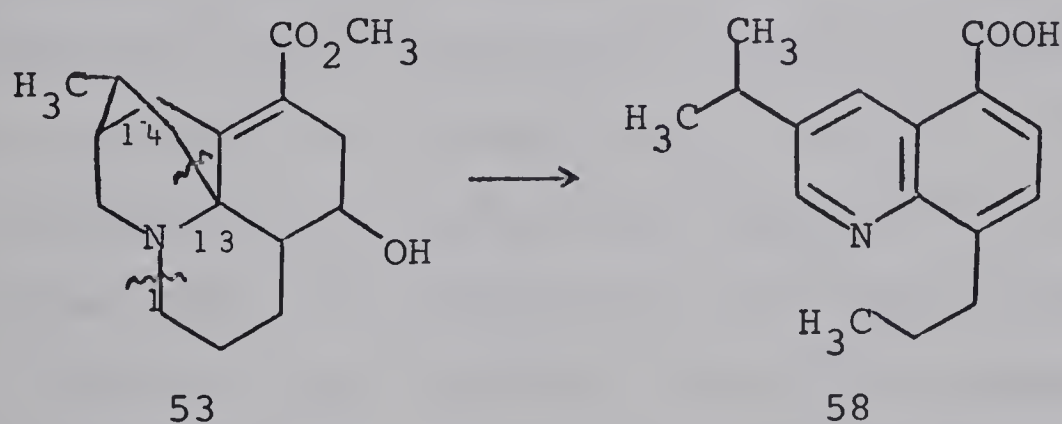






7

On the basis of the known structure and considering these three examples above one might expect annopodine under dehydrogenating conditions to be cleaved at the N - C-1, the C-13 - C-14 and the O - CH<sub>3</sub> bonds as shown below to yield 3-isopropyl-5-carboxy-8-n-propylquinoline (58).



53

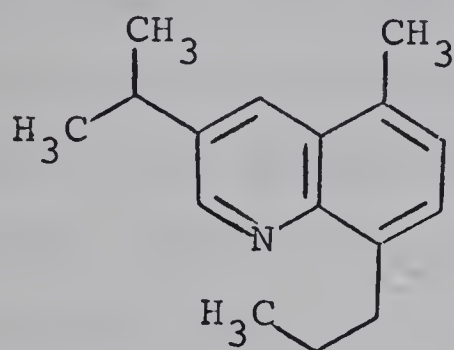
58

The initial selenium dehydrogenation of annopodine was conducted in an open vessel at temperatures up to 330°. A gas chromatographic separation on the crude dehydrogenation mixture yielded two products. The more polar component showed an apparent molecular ion at m/e 227(18) with the composition

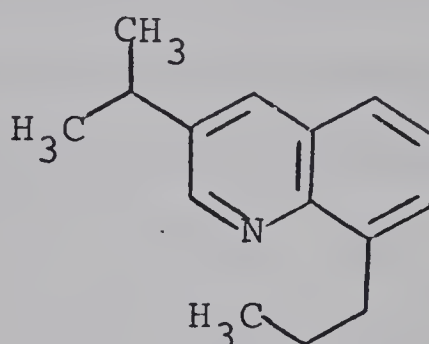




$C_{16}H_{21}N^*$ , while the less polar component showed a molecular ion at  $m/e$  213(24) with composition  $C_{15}H_{19}N$ . It is possible to speculate that the structures of these two dehydrogenation products may be represented by 59 and 60 respectively.



59



60

The mass spectra of each dehydrogenation product indicated the facile loss of a methyl radical to give an intense  $M^+-15$  fragment at  $m/e$  212(48) and  $m/e$  198(65), corresponding to  $C_{15}H_{19}N$  and  $C_{14}H_{16}N$ . This is consistent with the presence of the isopropyl group on an aromatic ring. However, the  $M^+-15$  fragment could have arisen from almost any alkyl side chain. Each product also exhibited an  $M^+-29$  fragment attributable to the loss of an ethyl radical from an alkyl side chain (prod. 59,  $m/e$  198(70) and prod. 60,  $m/e$  184(22)). Although these two simple fragmentation modes are consistent with the proposed structures they do not

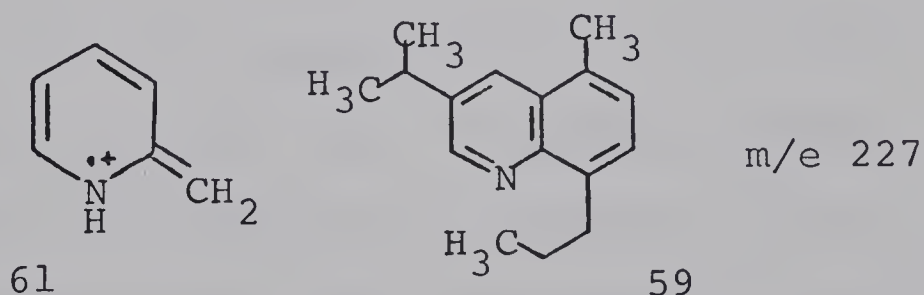
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\*All elemental compositions were determined by mass spectrometry.



offer any definitive evidence. The ultraviolet spectra of these dehydrogenation products are similar and are quinolinoid in nature.

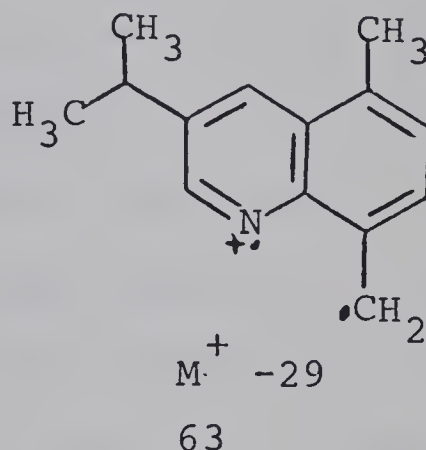
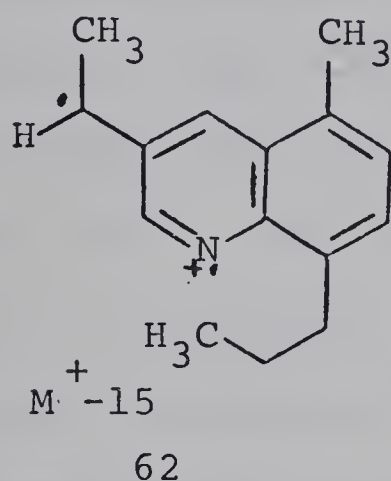
Another dehydrogenation on annopodine was carried out, this time in a sealed tube. Four components were isolated by ptlc on silica gel in differing degrees of purity and are listed in order of decreasing  $R_f$  value. All of the products have similar uv spectra which are again typical of a quinoline system. The least polar product showed an apparent molecular ion at  $m/e$  223(19) with the composition  $C_{16}H_{17}N$  and a base peak at  $m/e$  93(100) with the composition  $C_6H_7N$ . The peak  $m/e$  93,  $C_6H_7N$ , is frequently due to an ion of type 61, formed from an  $\alpha$  (or  $\gamma$ ) substituted pyridine. No satisfactory structure has



been derived for this product. The second component contained, according to its tlc behavior, one major basic component. From the spectral data it appears that this product is the quinoline 59. The mass spectrum showed a molecular ion at  $m/e$  227(46) with a base peak at  $m/e$  212(100) and other intense fragments



at  $m/e$  198(83) and 185(88). The two former fragments can be assigned respectively to the fragments 62 and 63. The  $M^+-CH_3$  fragment can arise by homolytic cleavage of a methyl radical from the isopropyl side chain or from the propyl side chain. The  $M^+-C_2H_5$  fragment must arise by loss of an ethyl radical from the propyl side chain. The  $M^+-C_3H_7$  fragment perhaps arises by the loss of ethylene from the  $M^+-15$  ion.

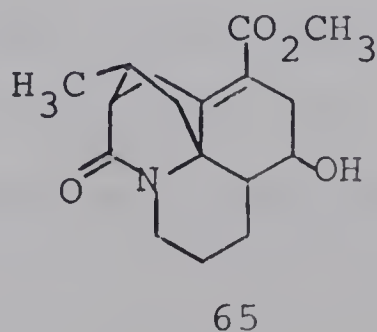
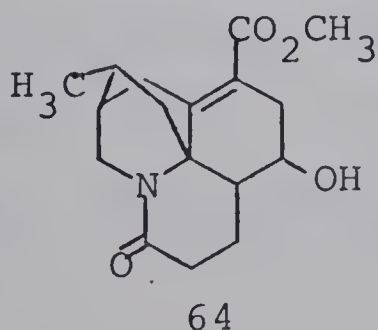


In agreement with the proposed structure for the dehydrogenation product, the nmr spectrum showed a multiplet at  $\tau$ 1.2 typical of a proton  $\alpha$  to the nitrogen in a quinoline ring, multiplets at  $\tau$ 2.25 and  $\tau$ 2.65 corresponding to the aromatic protons, a singlet at  $\tau$ 7.98 corresponding to the ring methyl, a doublet at  $\tau$ 8.64 corresponding to the isopropyl group, and a multiplet at  $\tau$ 9.07 presumably containing the terminal methyl of the n-propyl chain. The ultraviolet spectrum showed in neutral medium an intense absorption maximum at 228  $m\mu$  with



weak absorption maximum at 285  $m\mu$  and a shoulder at 320  $m\mu$ . In acidic medium the intense maximum shifted to 243  $m\mu$  with a weak maximum at 316  $m\mu$ . The other components of this dehydrogenation were obtained in small amounts and no firm conclusions could be drawn as to their nature (see experimental for details).

A selenium dioxide oxidation<sup>92</sup> of annopodine in refluxing aqueous dioxane yielded mainly a neutral compound. The infrared spectrum ( $\text{CHCl}_3$ ) showed that a carbonyl had been introduced  $\alpha$  to the nitrogen ( $1655\text{ cm}^{-1}$ ). The ultraviolet spectrum was similar to that of annopodine. The mass spectrum of this product showed a molecular ion at  $m/e$  305(2) which is in agreement with the introduction of a carbonyl oxygen at a methylene carbon. Acetylation of this material with acetic anhydride-pyridine yielded a product which showed a molecular ion at  $m/e$  347(51) and absorption in the infrared ( $\text{CCl}_4$ ) at  $1750\text{ cm}^{-1}$  consistent with the acetylation of the hydroxyl group present. The two possible structures for the lactam, based on the evidence at hand are shown as 64 and 65 below.

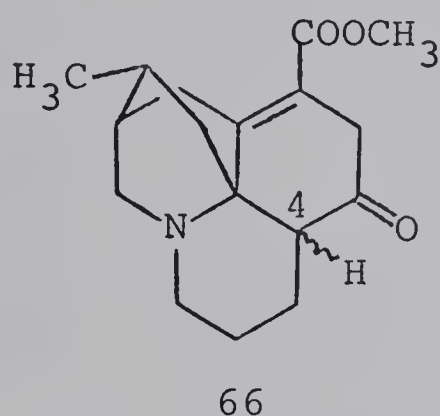








Oxidation of annopodine with Jones' reagent gave a product which failed to crystallize and which, according to tlc behavior, was composed of two components of similar  $R_f$  value. The infrared spectrum showed carbonyl absorption at 1710 and 1698  $\text{cm}^{-1}$ , and the ultraviolet spectrum showed absorption at 224  $\text{m}\mu$ , similar to that of annopodine itself. It is suggested that the dehydro compound is an equilibrium mixture of the ketones 66, epimeric at C-4. Treatment



of the mixture with perchloric acid - acetic acid effected no change.

An indication as to the number of protons  $\alpha$  to the ketone in dehydroannopodine was obtained by deuterium exchange. That annopodine itself does not have any readily exchangeable hydrogens other than that of the hydroxyl was shown by the mass spectrum of a sample which had been recovered from a  $\text{DCl-DOAc}$  treatment. Dehydroannopodine was subjected to



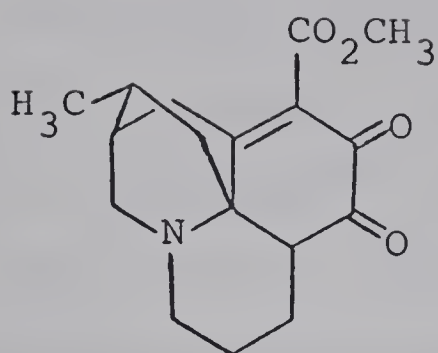
exchange in DCl-DOAc solution, then reduced with sodium borohydride in methanol-O-d. The mass spectrum of deuterated annopodine is compared with annopodine in Table 7. It appears that up to three atoms were incorporated. This is in agreement with the structure of dehydroannopodine.

TABLE 7

<u>Deuterated Alcohol</u>	<u>Annopodine</u>
m/e 295(2)	m/e 295 -
294(10)	294 -
293(23)	293 -
292(31)	292(4)
291(16)	291(22)
290 -	290(4)

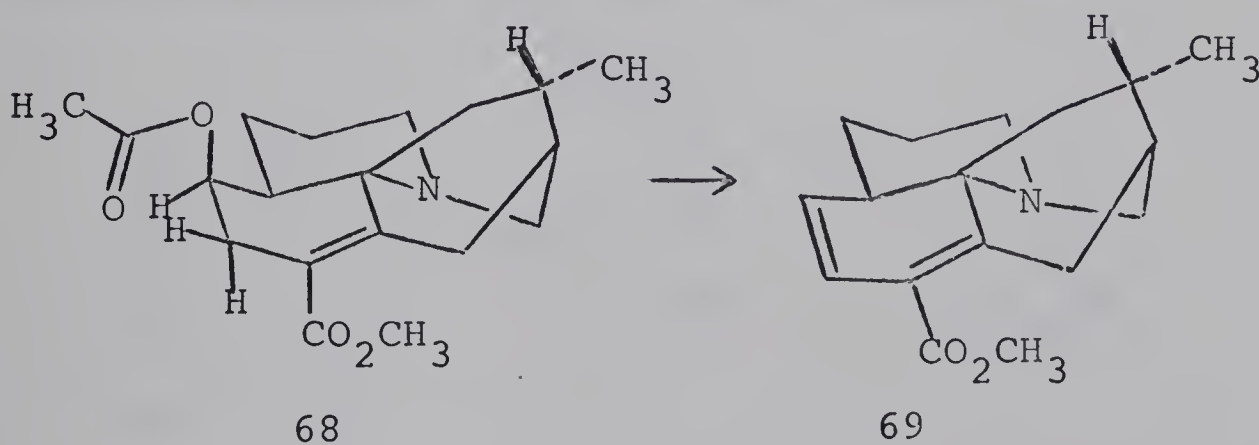
A selenium dioxide oxidation on crude dehydroannopodine was carried out in refluxing aqueous dioxane. The crude product was purified by column chromatography on alumina. The mass spectrum of the major basic product showed a molecular ion at m/e 319(9). The infrared spectrum ( $\text{CCl}_4$ ) showed absorption at 1750, 1725 and  $1680\text{ cm}^{-1}$ , possibly due to the formation of the 1,2-diketone 67.





67

Consideration of the stereochemistry of annopodine as determined by X-ray diffraction studies indicated that acetylannopodine should undergo cis elimination to yield a conjugated diene. Only one proton is orientated cis to the O-acetyl group, thus favoring elimination of the elements of acetic acid during pyrolysis as shown below.



68

69

The pyrolysis was carried out in a sealed tube at temperatures between 310 and 370°. The ultraviolet spectrum of the crude product showed a shoulder at 250-255 m $\mu$  in the ultraviolet. The expected con-



jugated diene chromophore should give a maximum in the region of 278  $m\mu$ , based on Fieser's modification of the Woodward diene rules<sup>87c</sup>, and considering the carbomethoxy group to be an alkyl substituent. The mass spectrum of the crude material did not show a molecular ion at  $m/e$  273 which would correspond to diene 69 or at  $m/e$  333 which corresponds to acetyl annopodine (68). The pyrolysis was not investigated further.

The mass spectra of annopodine and dehydroannopodine are interpretable on the basis of the structure presented for annopodine. In Table 8 the major fragments observed in annopodine are given. The compositions of some of the ions were determined by exact mass measurements and these are listed.

TABLE 8

$m/e$	%BP	E.M.	$m/e$	%BP	E.M.
291	22	$C_{17}H_{25}NO_3$	248	100	$C_{14}H_{18}NO_3$
276	6		216	8	$C_{13}H_{14}NO_2$
249	25				

Metastable peaks were observed at  $m/e$  211.3 corresponding to 291 $\rightarrow$ 248 and at  $m/e$  188.3 corresponding to 248 $\rightarrow$ 216. A fragmentation scheme for annopodine is presented in Scheme 17. Two possible routes are outlined to the  $m/e$  248 and  $m/e$  216 fragments.





SCHEME 17

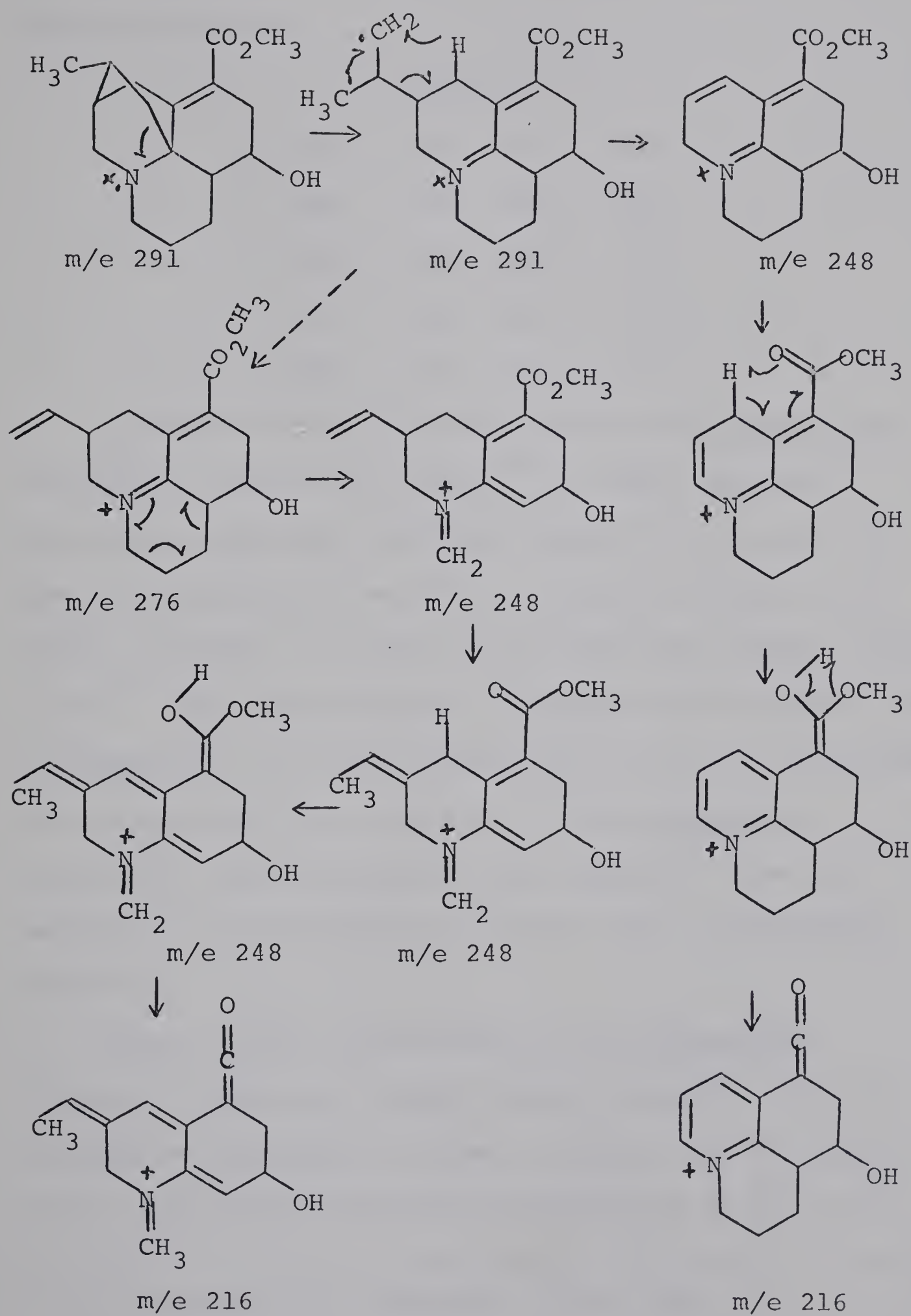




Table 9 lists the major fragments observed for dehydroannopodine.

TABLE 9

m/e	%BP	m/e	%BP
289	64	246	100
274	16	219	39
261	19	218	79
247	21	214	22

A scheme for the biosynthesis of the Lycopodium alkaloids, proposed by Conroy<sup>79</sup> in 1960, suggests that these alkaloids could be formed in the plant by the condensation of two 3,5,7- triketo-octanoic acid chains 70 which, in turn are derived from acetate units. Leete<sup>93</sup> has observed some incorporation of acetate into L. annotinum. In this laboratory it has been suggested\* that lysine may be a precursor of the Lycopodium alkaloids. Recently, MacLean and Spenser<sup>94</sup> have observed the incorporation of lysine into a Lycopodium alkaloid.

Based on the biosynthesis of the Lycopodium alkaloids involving acetate units, annopodine may be thought to originate as shown in Scheme 18. An initial aldol condensation between the methylene at C-12 and

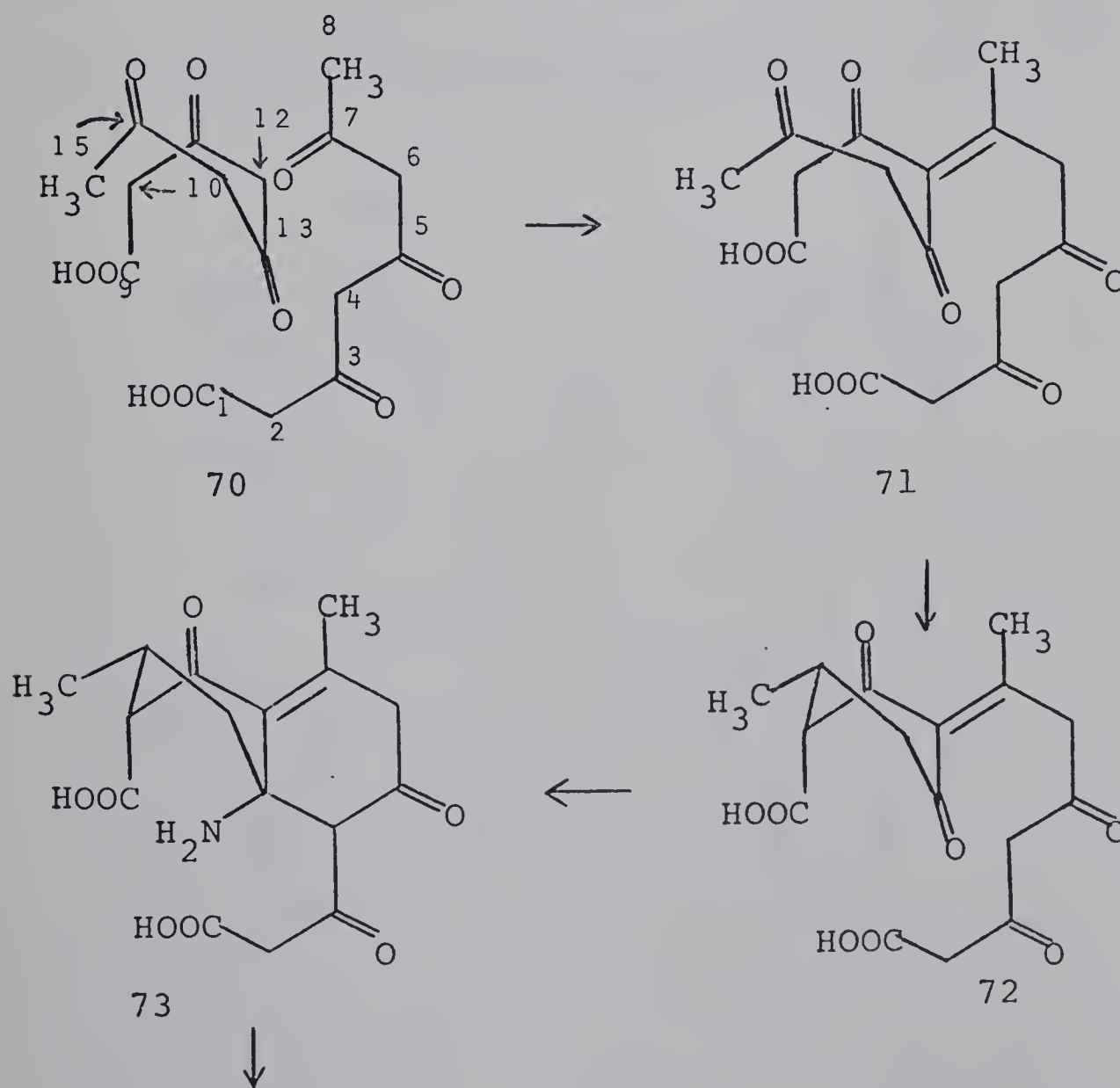
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\* G.G. Iverach, Ph.D. Thesis, U. of A., 1963.



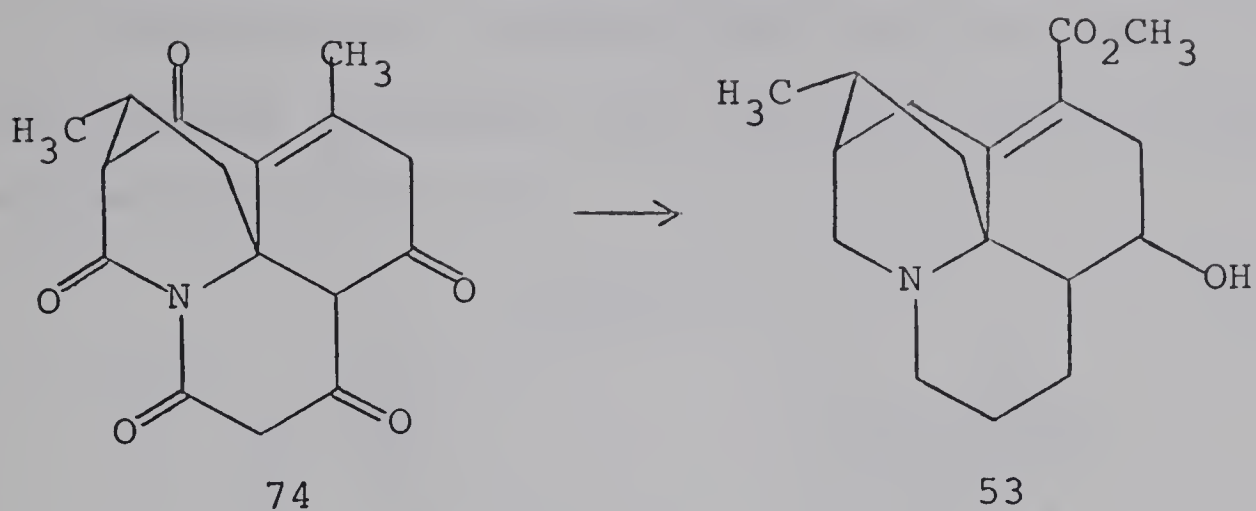
the C-7 carbonyl followed by dehydration towards C-12 leads to 71. A second aldol condensation between C-10 and C-15 followed by dehydration and reduction gives 72. A Mannich reaction on 72 involving the C-13 carbonyl, the C-4 methylene and ammonia leads to the nitrogenous intermediate 73 which on ring closure gives 74. Adjustment of the oxidation level followed by methylation of the carboxyl group formed at C-7 gives annopodine. This order of steps is of course arbitrary.

SCHEME 18

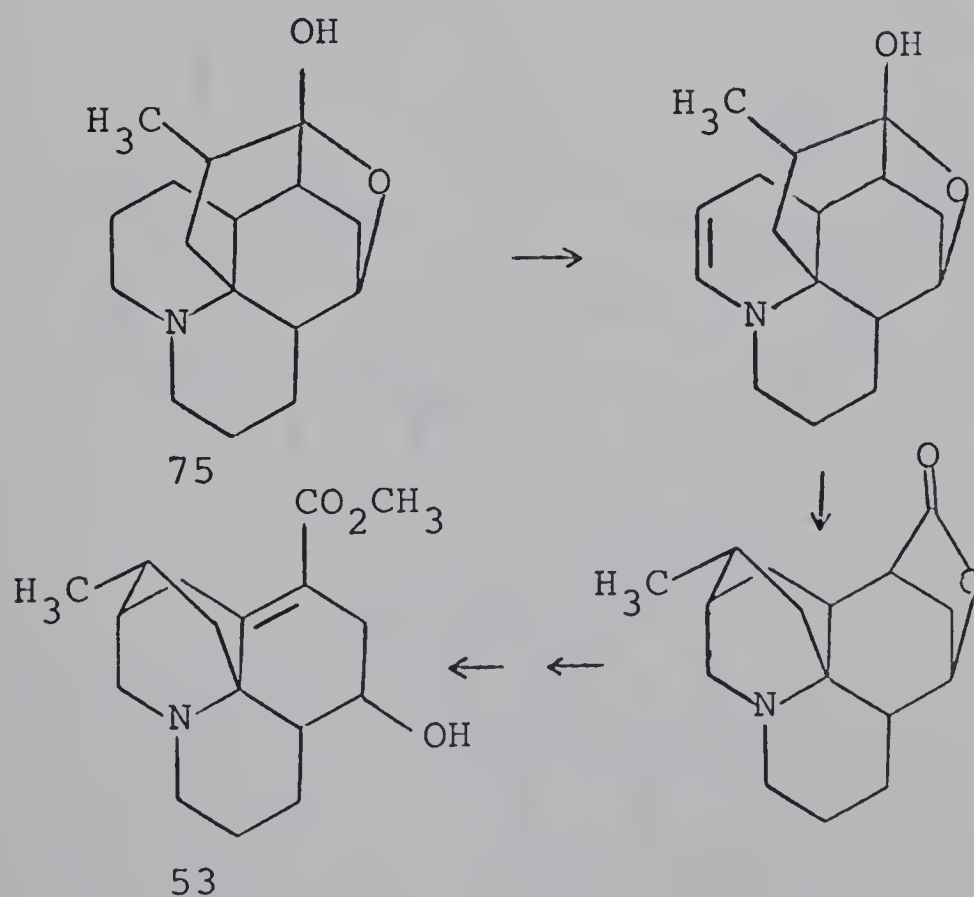




## SCHEME 18 (cont.)



The biosynthetic route for annopodine derived from lysine is rendered more plausible<sup>94</sup>. Annopodine can be generated from the same common intermediate 75 that leads to the various Lycopodium alkaloids<sup>121</sup>.

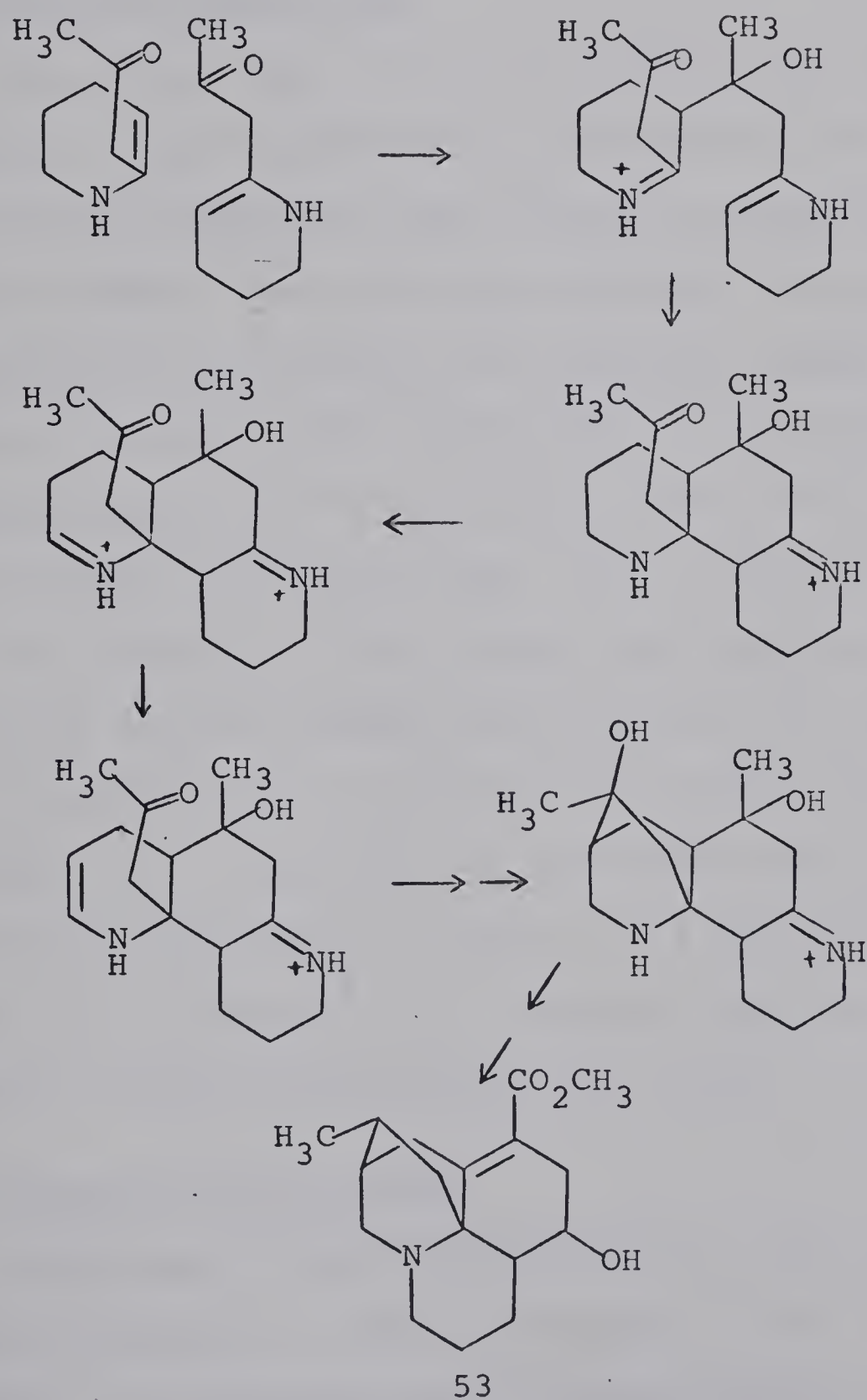






Alternatively a scheme which does not involve an intermediate lycopodine-type skeleton may be written as shown in Scheme 20.

SCHEME 20





## EXPERIMENTAL

## SECTION TWO

1. Annopodine Methiodide

Annopodine (5mg) in methyl iodide (1 ml) and methanol (7 ml) was heated at reflux for 4 hr. The solvent was evaporated under reduced pressure and acetone added. Crystals were obtained. The mother liquors were pipetted off, the crystals washed with a small volume of cold acetone-ether (1:1), then recrystallized from hot acetone: mp 240.5-242° - fine needles; ir (Nujol) 3320, 1720, 1630  $\text{cm}^{-1}$ .

The density of the crystals was determined by achieving neutral buoyancy for a crystal in a mixture of chlorobenzene ( $d = 1.1\text{g/cm}^3$ ) and carbon tetrachloride ( $d = 1.6\text{g/cm}^3$ ), and then measuring the density of the mixture. Found:  $d = 1.402 \pm 0.002\text{g/cm}^3$ ; Calcd:  $d = 1.242\text{g/cm}^3$ ,  $d = 1.410\text{g/cm}^3$  when one molecule of acetone is present per unit cell.

2. Annopodine Hydrobromide

Anhydrous HBr was bubbled briefly into a solution of annopodine (15mg) in methanol (1 ml). The solvent was evaporated under reduced pressure and



the residual foamy solid dissolved in a 1:1 mixture of EtOAc-CH<sub>2</sub>Cl<sub>2</sub> (5 ml). When most of the CH<sub>2</sub>Cl<sub>2</sub> was boiled off and the remaining solution was allowed to cool slowly, crystallization occurred. The crystals were dried under vacuum at room temperature: mp 230.5-232.5°.

The density of the crystals was determined in the same manner as for the methiodide. Found:  $d = 1.423 \pm 0.002 \text{g/cm}^3$ ; Calcd:  $d = 1.465 \text{g/cm}^3$ .

### 3. Selenium Dehydrogenation of Annopodine(Open Tube)

A mixture of annopodine (30mg) and powdered selenium (120mg) in a tube sealed at one end was heated in a Wood's metal bath for 2 hr during which time the temperature of the bath was raised from 100° to 330°. The CH<sub>2</sub>Cl<sub>2</sub> soluble material which distilled to the cooler part of the tube was collected (6mg) and distilled (bath temperature 60-80°, 0.02 mm). A gas chromatographic purification was carried out using a 10% QF-1, 5' x  $\frac{1}{8}$ " 60/80 Chromo W column and yielded two apparently homogeneous (single peak on the gc) fractions.

Product with longer retention time (59): uv max (EtOH) 280, 228, 219(sh) m $\mu$ ; uv max (EtOH, H<sup>+</sup>) 283, 240(sh), 228, 210 m $\mu$ ; mass spectrum m/e 227(C<sub>16</sub>H<sub>21</sub>N, 18), 212(48), 198(C<sub>14</sub>H<sub>16</sub>N, 70),



185(19), 170(19), 169( $C_{13}H_{13}$ , 100).

Product with shorter retention time (60): uv max (EtOH) 280, 228, 219(sh)  $m\mu$ ; uv max (EtOH,  $H^+$ ) 283, 240(sh) 228, 210  $m\mu$ ; mass spectrum  $m/e$  213( $C_{15}H_{19}N$ , 24), 198( $C_{14}H_{16}N$ , 65), 185(22), 184(22), 173(52), 172(59), 170( $C_{13}H_{14}$ , 100), 155(59).

In both cases the base peak is thought to be due to a substituted naphthalene impurity. The ultra-violet spectra of naphthalenes and quinolines are very similar<sup>87b</sup>.

#### 4. Selenium Dehydrogenation of Annopodine (Sealed Tube)

A mixture of annopodine (47mg) and powdered selenium (230mg) in a thick walled glass tube, sealed under vacuum, was heated slowly in an aluminum block to 310° and held at this temperature for 0.5 hr. The tube was cooled, broken in two and the volatile components (15mg) distilled out at 50-230° (0.03 mm). The distillate was purified by ptlc on 0.5 mm silica gel plates ( $CHCl_3$ - $CH_3OH$ , 92:8).

Least polar prod: tlc -  $SiO_2$  ( $CH_2Cl_2$ - $CHCl_3$ , 1:1) - one basic component, i.e. Dragendorff positive, two minor neutral impurities; uv max (EtOH) 330, 320, 305, 297, 285, 275, 238(sh), 230, 210(sh)  $m\mu$ ; uv max (EtOH,  $H^+$ ) 320, 307, 240(sh), 230, 203  $m\mu$ ; mass spectrum  $m/e$  223( $C_{16}H_{17}N$ , 19), 194( $C_{14}H_{12}N$ , 30),





185(13), 163(10), 93(100).

Product 59: tlc -  $\text{SiO}_2(\text{CHCl}_3)$  - one basic component, two neutral impurities; ir ( $\text{CCl}_4$ ) 3080-3020 (aromatic C-H), 1500 (aromatic C=C)  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 1.2 (m, 1,  $\alpha$ -pyridine  $\text{CH}$ ), 2.25, 2.65 (c, 2-3,  $\gamma$ -pyridine and aromatic  $\text{CH}$ ), 6.8-7.8 (c, 2-3 benzylic protons) 7.98 (s, 3, aromatic  $\text{CH}_3$ ), 8.64 (d, 6,  $J=8$  cps,  $(\text{CH}_3)_2\text{CH}$ ), 9.08 (m, 3,  $\text{CH}_3\text{-CH}$ ); uv max (EtOH) 320, 306, 295, 285, 231  $\text{m}\mu$ ; uv max (EtOH,  $\text{H}^+$ ) 317, 243  $\text{m}\mu$ ; mass spectrum m/e 227(46), 226(35), 213(54), 212(100), 198(83), 185(88), 171(37), 170(39), 157(78), 156(30), 143(72).

Third prod: tlc -  $\text{SiO}_2(\text{CHCl}_3\text{-CH}_3\text{OH}, 49:1)$  - two basic components with very similar  $R_f$  values; uv max (EtOH) 320, 278, 273, 231, 210  $\text{m}\mu$ ; uv max (EtOH,  $\text{H}^+$ ) 318, 280, 240(sh), 231, 204  $\text{m}\mu$ ; mass spectrum m/e 215( $\text{C}_{15}\text{H}_{21}\text{N}$ , 13), 200(16), 185(16), 173(15), 160(22), 146( $\text{C}_{10}\text{H}_{12}\text{N}$ , 100).

Most polar prod: tlc -  $\text{SiO}_2(\text{CHCl}_3\text{-CH}_3\text{OH}, 49:1)$  - one basic component; ir ( $\text{CCl}_4$ ) 1740 (C=O), 1700 (C=O), 1580, 1500 (w, aromatic)  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 1.2 (m, 1,  $\alpha$ -pyridine  $\text{CH}$ ), 2.2-2.8 (c, 2-3, aromatic  $\text{CH}$ ), 5.85 (m, 1-2, ?), 7.52, 7.57 (two s, 4-6, aromatic  $\text{CH}_3$ ), 8.2-9.0 (c), 9.15 (m); uv max (EtOH) 351, 334, 319(sh), 274, 235, 219  $\text{m}\mu$ ; uv max (EtOH,  $\text{H}^+$ ) 288,



237(sh), 231, 215 m $\mu$ ; mass spectrum m/e 261(C<sub>17</sub>H<sub>27</sub>NO, 10), 247(10), 221(C<sub>16</sub>H<sub>15</sub>N, 13), 208(16), 207(C<sub>15</sub>H<sub>13</sub>N, 100), 206(19), 193(17), 192(C<sub>14</sub>H<sub>10</sub>N, 34), 191(14).

##### 5. Selenium Dioxide Oxidation of Annopodine

To a solution of annopodine (8mg) dissolved in dioxane (15 ml) was added freshly sublimed selenium dioxide (24mg) which had been dissolved in 5-6 drops of H<sub>2</sub>O and diluted with dioxane (2 ml). The reaction mixture was refluxed for 18 hr, then the solvent was evaporated under reduced pressure, the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub> and extracted with dil aq HCl. The acidic extract was made basic with dil NH<sub>4</sub>OH, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried (MgSO<sub>4</sub>), filtered and the filtrate evaporated yielding 1.5mg of material which was not investigated. The methylene chloride layer was dried (MgSO<sub>4</sub>), filtered and the filtrate evaporated yielding 7.5mg of material: tlc - Al<sub>2</sub>O<sub>3</sub>(CHCl<sub>3</sub>-CH<sub>3</sub>OH, 99:1) - one major neutral component; ir (CHCl<sub>3</sub>) 3615 (OH), 1715 (ester C=O), 1660 (lactam C=O) cm<sup>-1</sup>; uv max (EtOH) and (EtOH, H<sup>+</sup>) 226 m $\mu$ ; mass spectrum m/e 305 (1.5), 303(2.5), 301(4.5), 287(22), 286(16), 257(13), 230(16), 186(22), 144(100).

The product was acetylated under the usual conditions for 14 hr. The reaction mixture was



evaporated to dryness under reduced pressure, the residue dissolved in  $\text{CH}_2\text{Cl}_2$  and extracted with dil  $\text{NH}_4\text{OH}$ , the methylene chloride layer dried ( $\text{MgSO}_4$ ), filtered and the filtrate evaporated: tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ ) - one major neutral component, a few minor impurities; ir ( $\text{CCl}_4$ ) 1750 (acetyl  $\text{C}=\text{O}$ ), 1725 (ester  $\text{C}=\text{O}$ ), 1680 (lactam  $\text{C}=\text{O}$ ), 1650 ( $\text{C}=\text{C}$ )  $\text{cm}^{-1}$ ; mass spectrum m/e 348(11), 347( $\text{C}_{19}\text{H}_{25}\text{NO}_5$ , 51) 245(56), 186(100), 158(29).

#### 6. Dehydroannopodine (66)

To a cold ( $0^\circ$ ) solution of annopodine (9mg) dissolved in acetone (5 ml) there was added dropwise with stirring an excess of Jones' reagent (Standard solution: 26.72g of  $\text{CrO}_3$  and 23 ml of  $\text{H}_2\text{SO}_4$  diluted to 100 ml with  $\text{H}_2\text{O}$ ). The reaction mixture was stirred at room temperature for 24 hr then diluted with  $\text{H}_2\text{O}$ . After evaporation of the acetone under reduced pressure, dil  $\text{NH}_4\text{OH}$  was added and the basic solution extracted with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried ( $\text{MgSO}_4$ ), filtered and the filtrate evaporated yielding 9mg of crude ketone 66: tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ ), tlc -  $\text{SiO}_2$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 93:7) - two major products, one minor product; ir ( $\text{CCl}_4$ ) 1725 (ester, ketone  $\text{C}=\text{O}$ ), 1640 ( $\text{C}=\text{C}$ )  $\text{cm}^{-1}$ ; uv max (EtOH) 224 m $\mu$ ; uv max (EtOH,  $\text{H}^+$ ) 226 m $\mu$ ; mass spectrum m/e 289(63), 274(16),





261(19), 247(20), 246(100), 232(19), 230(18), 219(38), 218(78).

### 7. Deuterioannopodine

The crude, distilled (100-150°, 0.3 mm) dehydroannopodine (7mg), dissolved in 1.5 ml of DCl-DOAc (DCl-D<sub>2</sub>O-Ac<sub>2</sub>O) was allowed to stand at room temperature for 3 hr. The solvent was then removed under reduced pressure and methylene chloride was added to the residue followed by a dil solution of Na<sub>2</sub>CO<sub>3</sub> in D<sub>2</sub>O(2-3 ml). The mixture was shaken, the CH<sub>2</sub>Cl<sub>2</sub> layer separated, dried (MgSO<sub>4</sub>), filtered and the filtrate evaporated yielding a residue which was immediately dissolved in fresh DCl-DOAc solution. From the reaction mixture, after the second treatment, 7mg of material was obtained which was dissolved in CH<sub>3</sub>OD (1 ml) and stirred in the presence of a few milligrams of NaBH<sub>4</sub> for 48 hr at room temperature. The reaction mixture was then diluted with aq NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The dried (MgSO<sub>4</sub>), filtered, evaporated filtrate yielded 6mg of deuterioannopodine: tlc - Al<sub>2</sub>O<sub>3</sub>(CHCl<sub>3</sub>-CH<sub>3</sub>OH, 99:1) - one component, not identical in R<sub>f</sub> with annopodine; mass spectrum m/e 295(2), 294(10), 293(23), 292(31), 291(16), 290(4), 250(38), 249(100), 248(44), 236(12),





235(17), 234(13), 217(8), 191(9).

The mass spectrum of annopodine was determined under similar conditions: mass spectrum  $m/e$  292(4), 291(22), 290(4), 249(25), 248(100), 216(7), 190(6).

#### 8. Selenium Dioxide Oxidation of Dehydroannopodine

To a solution of crude, distilled dehydroannopodine (8mg) dissolved in dioxane (15 ml) was added freshly sublimed selenium dioxide (8mg) which was dissolved in 5-6 drops of  $H_2O$  and diluted with a few milliliters of dioxane. The reaction mixture was refluxed for 4 hr, then the solvent was evaporated under reduced pressure and the residue dissolved in methylene chloride, and this was extracted with dil  $NH_4OH$ . The dried ( $MgSO_4$ ), filtered  $CH_2Cl_2$  layer, after removal of the solvent yielded 5mg of material which was chromatographed on alumina (0.5g). The fraction eluted with ether -  $CH_2Cl_2$  (1:1) contained product 67: tlc -  $Al_2O_3(CHCl_3)$  - essentially one basic component; ir ( $CCl_4$ ) 1750, 1720 ( $\alpha$ -diketone  $C=O$ ), 1680 (ester  $C=O$ ), 1650 ( $C=C$ )  $cm^{-1}$ ; mass spectrum  $m/e$  319(9), 306(16), 305(81), 290(14), 277(18), 274(14), 273(19), 246(24), 234(13), 218(13), 217(14), 190(13), 174(18), 162(18).



### 9. Acetylannopodine (68)

Annopodine (20mg) was acetylated under the usual conditions for 20 hr, the solvent was evaporated under reduced pressure and the residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and extracted with dil aq  $\text{NaHCO}_3$ . The methylene chloride layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and the filtrate evaporated yielding a residue which was chromatographed on alumina (lg, 15 ml fractions). The product was eluted with ether: tlc ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 99:1) - homogeneous; ir ( $\text{CCl}_4$ ) 1740 (acetyl  $\text{C}=\text{O}$ ), 1725 (ester  $\text{C}=\text{O}$ ), 1635 ( $\text{C}=\text{C}$ )  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 4.92 (m, 1,  $W/2 = 10$  cps,  $\text{CH}-\text{OAc}$ ), 6.34 (s, 3,  $\text{OCH}_3$ ), 6.8-7.8 (c, 8,  $-\text{CH}_2-\text{C}=\text{C}$  and  $-\text{CH}_2-\text{N}$ ), 8.2 (s, 3,  $\text{CH}_3-\text{CO}-$ ), 8.1-8.8 (c, 9), 8.9 (d, 3,  $J=6$  cps,  $\text{CH}_3-\text{CH}$ ).

### 10. Pyrolysis of Acetylannopodine (68)

Acetylannopodine (14mg), dissolved in 1 ml of methylene chloride, was deposited on  $\frac{1}{8}$ " glass beads contained in a small glass tube by evaporation of the solvent. The tube was sealed under vacuum and heated over a period of 50 min from 310 to 370°. The tube was cooled, broken in two and the volatile contents distilled out (140-170°, 0.04 mm): tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ ) - one basic product, numerous minor products; uv max (EtOH) 255-250(sh) m $\mu$ .



11. Mass Spectrum of Annopodine

Mass spectrum m/e 291( $C_{17}H_{25}NO_3$ , 22), 276(6),  
274(5), 260(5), 249(25), 248( $C_{14}H_{18}NO_3$ , 100), 234  
 $C_{13}H_{16}NO_3$ , 12), 216( $C_{13}H_{14}NO_2$ , 7), 190( $C_{12}H_{16}NO$ , 6),  
188( $C_{12}H_{14}NO$ , 5).



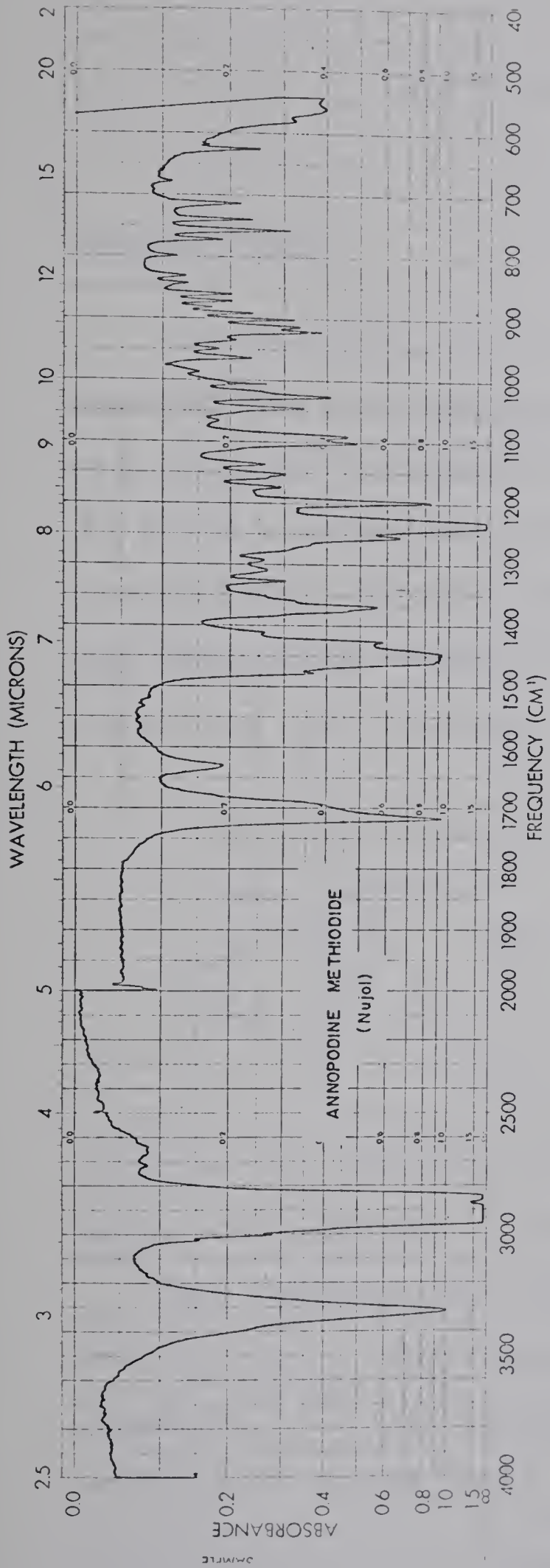


FIGURE 13

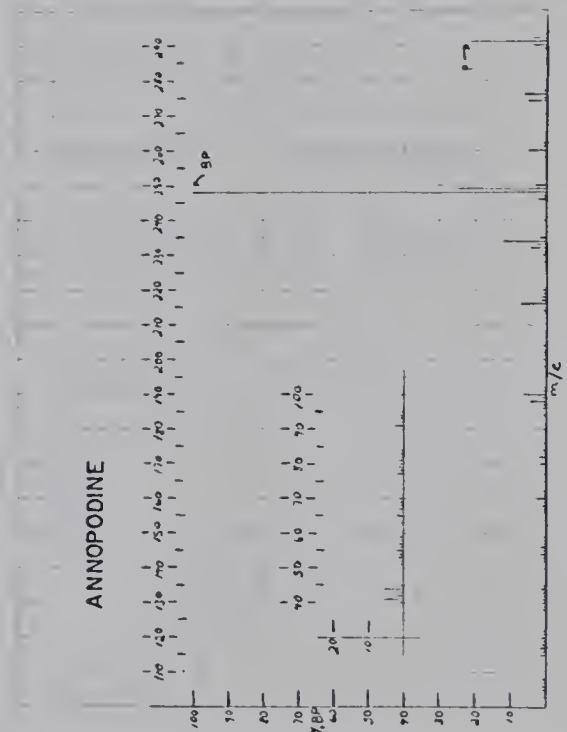


FIGURE 14

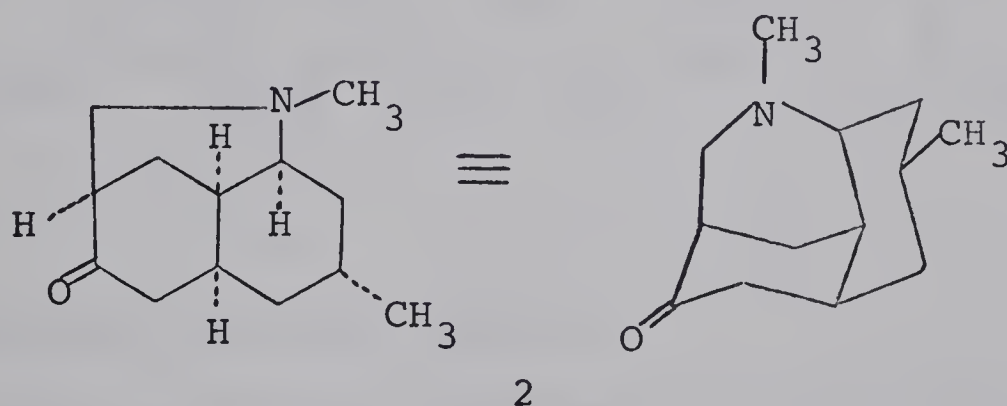




## DISCUSSION AND RESULTS

## SECTION THREE

An alkaloid  $C_{13}H_{21}NO$ , perchlorate mp 194-196°, was isolated from Lycopodium lucidulum Michx. by D.S. Nkunika<sup>61</sup> and named luciduline. This alkaloid is thought to be identical with alkaloid L.21, isolated from the same species by Manske<sup>5</sup>. Spectral and degradation studies\* led to the tentative structure 2 for this alkaloid. In order to prove or



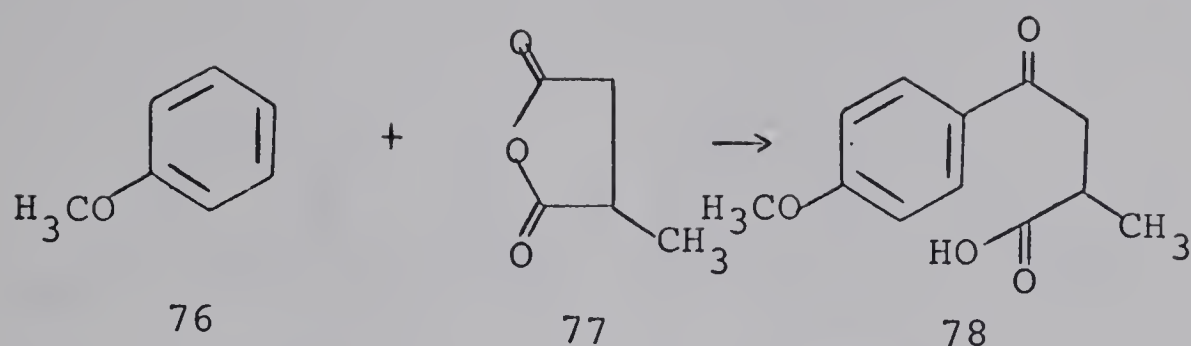
disprove the structural and stereochemical assignment, the synthesis of compound 2 was undertaken.

The starting point for the synthesis was anisole (76). Condensation with methylsuccinic anhydride<sup>95,96</sup> (77) yielded  $\alpha$ -methyl- $\beta$ -anisoylpropionic acid<sup>97</sup> (78) in 65% yield.

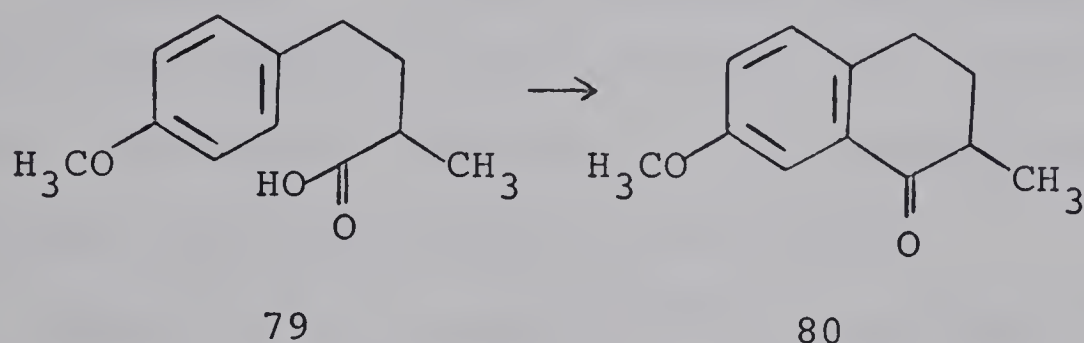
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\* D.S. Nkunika, Ph.D. Thesis, U. of A., 1966.





Clemmensen reduction<sup>97,98</sup> of the keto group in  $\alpha$ -methyl- $\beta$ -anisoylpropionic acid yielded  $\alpha$ -methyl- $\gamma$ -(p-methoxyphenyl)butyric acid<sup>97</sup> (79) which was obtained in 82% yield. The mass spectrum showed the

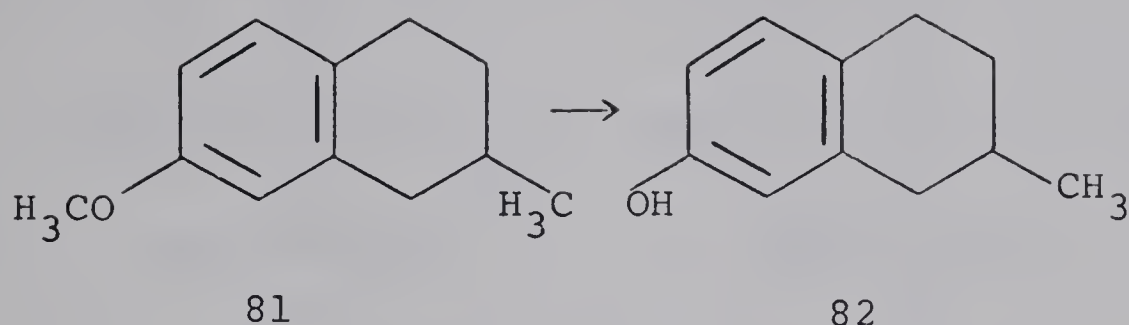


molecular ion at  $m/e$  208(15).

The acid 79 was cyclized to 1-keto-2-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene<sup>97</sup> (80) with phosphorous pentoxide. After distillation of the crude material, ketone 80 was obtained in 46% yield.

Reduction of the carbonyl in 80 was carried out in the same manner as for the reduction of 78. A 52% yield of 2-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene<sup>97</sup> (81) was obtained.



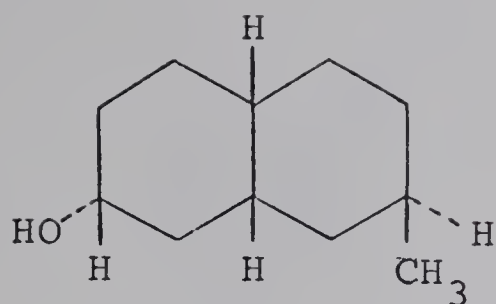


At this point in the synthesis it was felt that the cis-fused compound might be conveniently prepared by cleavage of the ether followed by catalytic hydrogenation of the phenol.

Cleavage<sup>99a,b</sup> of the ether 81 was effected in a mixture of refluxing glacial acetic and hydrobromic acids. 2-Methyl-7-hydroxy-1,2,3,4-tetrahydronaphthalene (82) was obtained in 87% yield.

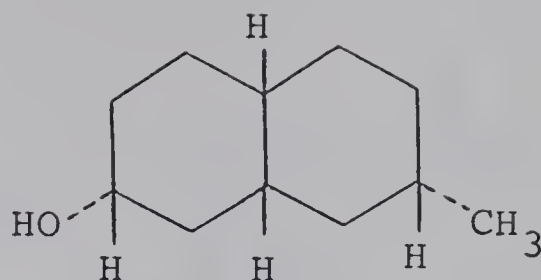
Catalytic hydrogenation<sup>100</sup> of the phenol was carried out at 110° under high pressure using ruthenium on charcoal as the catalyst. A thin layer chromatogram on the crude hydrogenation product indicated a mixture of products. Assuming that cis hydrogenation of the phenol ring has taken place, there would be two possible epimers 83 and 84 as products. It is also possible that the hydrogenation proceeds through an enol, which can equilibrate to the ketone, which then can hydrogenate from either the syn or anti side. In so doing the stereospecificity





syn-cis-anti

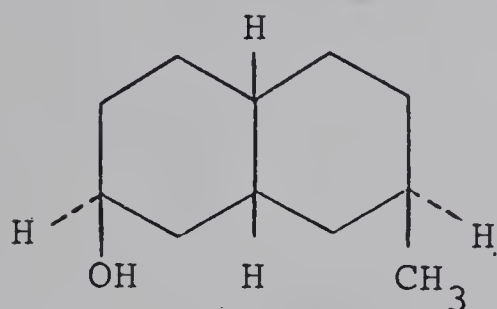
83



syn-cis-syn

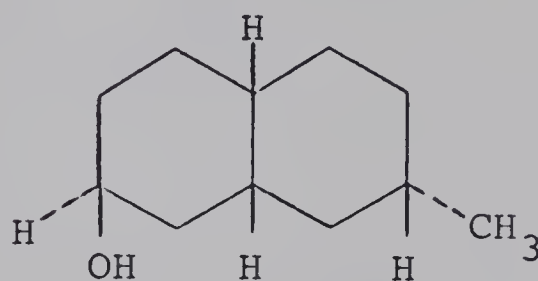
84

at the hydroxyl carbon is lost. This means that the two products 85 and 86 are also possible. A cis-fused



anti-cis-anti

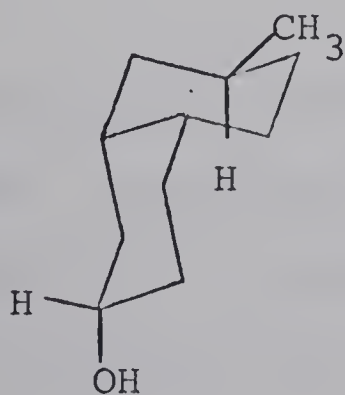
85



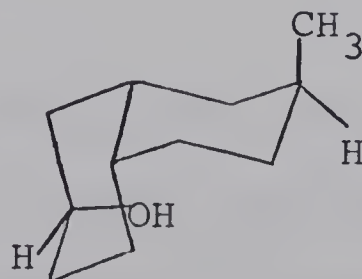
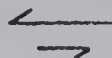
anti-cis-syn

86

decalin may exist in two conformers. The preferred conformation usually depends on the steric repulsion of the substituents. Thus for each of the four cis-fused decalin alcohols we may draw two conformers as shown below.



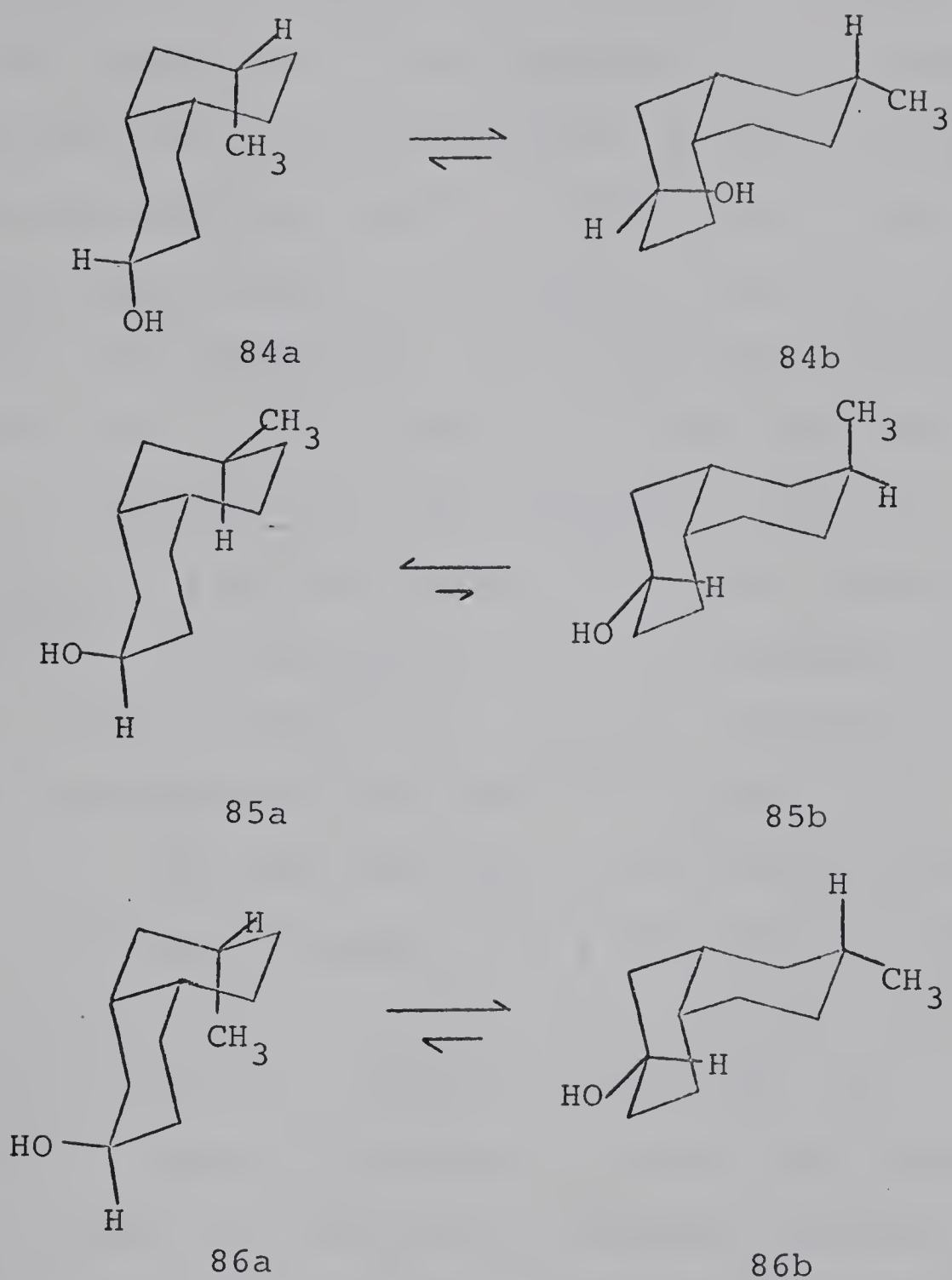
83a



83b







The preferred conformers are probably 83a, 84b, 85a and 86b. The energy difference between conformers 84a and 84b is probably small, however 84b is probably preferred due to the smaller space requirement<sup>67a</sup>



(A value, 0.7 kcal) of the hydroxyl group compared with that of the methyl group (A value, 1.7 kcal).

The separation of the components in the crude hydrogenation mixture was achieved by means of column chromatography over alumina. Three alcohols were isolated which appeared according to their tlc behavior to be homogeneous. The least polar alcohol, a solid, mp 71.5-73°, showed in its nmr spectrum ( $\text{CCl}_4$ ) a multiplet at  $\tau 6.07$  ( $W/2=8\text{cps}$ ) which is typical of a hydrogen geminal to an axial hydroxyl group<sup>120</sup>. In disagreement with the assignment of an axial alcohol grouping, the infrared spectrum ( $\text{CCl}_4$ ) showed absorption at  $1040\text{ cm}^{-1}$ \*<sup>67b</sup> as well as at  $3600\text{ cm}^{-1}$ . The mass spectrum of this alcohol showed its highest mass fragment at  $m/e$  150 presumably due to the facile loss of  $\text{H}_2\text{O}$  from the molecular ion. Two cis-fused axial alcohols, 84b and 85a, are possible. Since this alcohol is eluted very readily from alumina it is tentatively assigned structure 84b, in which the hydroxyl group is less exposed than in 85a. The second alcohol, a semi-crystalline solid, showed in its nmr spectrum a multiplet at  $\tau 6.07$

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\* Axial alcohols are reported to have strong absorption for the C-O stretch at  $996\text{-}1036\text{ cm}^{-1}$  while equatorial alcohols have strong absorption at  $1037\text{-}1044\text{ cm}^{-1}$ .

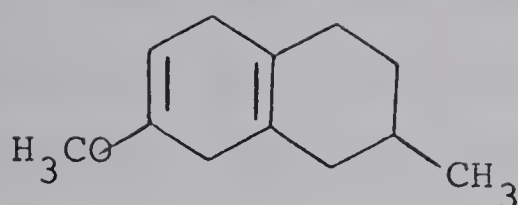


( $W/2=8\text{cps}$ ), again typical of a hydrogen geminal to an axial hydroxyl group. The infrared spectrum ( $\text{CCl}_4$ ) showed absorption at  $985\text{ cm}^{-1}$  and  $3600\text{ cm}^{-1}$  in agreement with an axial alcohol. The mass spectrum showed the highest mass peak at  $m/e$  150. This alcohol is assigned structure 85a. The most polar alcohol, an oil, showed in its nmr spectrum ( $\text{CCl}_4$ ) a multiplet at  $\tau 6.4$  ( $W/2=25\text{cps}$ ) and in its ir spectrum ( $\text{CCl}_4$ ), absorption at  $1040\text{ cm}^{-1}$  typical of a proton geminal to an equatorial hydroxyl group. This alcohol was assigned structure 83a or 86b.

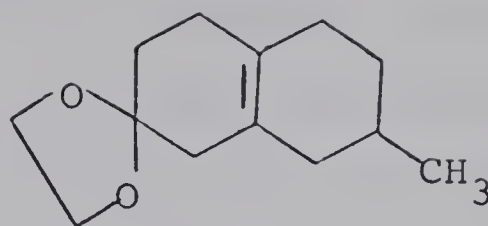
The three alcohols were oxidized with Jones' reagent to the respective ketones. If the structural assignments are correct the ketones from alcohols 83a and 85a should be identical as should those from 84b and 86b. The ir spectrum of each of the ketones was determined and all were found to be different. Thus it appeared that at least one of the alcohols possessed a trans-decalin structure. An alternate route was decided upon.

2-Methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (81) was subjected to Birch reduction<sup>101</sup>. The product, 1,4-dihydro-2-methoxy-7-methyl-5,6,7,8-tetrahydronaphthalene (87), was obtained in 93% yield. The nmr spectrum ( $\text{CCl}_4$ ) of 87 showed a one proton, poorly





87



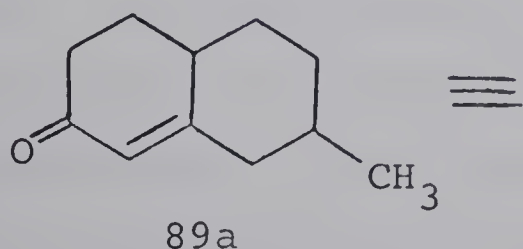
88

resolved triplet at  $\tau$ 5.55 assigned to the olefinic proton, a three proton singlet at  $\tau$ 6.58 assigned to the methyl ether and a doublet at  $\tau$ 9.05 ( $J=5$  cps) assigned to the secondary methyl group.

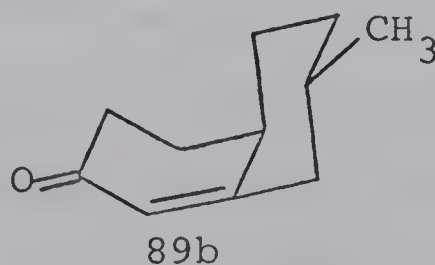
The enol ether was converted into the ethylene ketal 88. The mass spectrum indicated a molecular ion at  $m/e$  208(41) with exact mass corresponding to  $C_{13}H_{20}O_2$ .

High pressure hydrogenation of the ketal using Ru/C gave a mixture of three products. The mixture, after hydrolysis, showed hydroxyl absorption in the infrared and did not show carbonyl absorption. This route was abandoned.

A more direct route for arriving at the cis-fused ring system involves the  $\alpha,\beta$ -unsaturated ketone 89 obtained from the Birch reduction product 87. The



89a



89b





enol ether was hydrolyzed<sup>102</sup> in refluxing aqueous methanolic hydrochloric acid to give the ketone in 95% yield. The infrared spectrum ( $\text{CCl}_4$ ) of the product showed weak absorption at 1725 and strong absorption at  $1680\text{ cm}^{-1}$ , corresponding to approximately 80%  $\alpha,\beta$ - and 20%  $\beta,\gamma$ -unsaturated ketone. Absorption at  $1625\text{ cm}^{-1}$  is attributed to the carbon-carbon double bond. Careful fractional distillation achieved some purification of the  $\alpha,\beta$ -unsaturated ketone. Increasing the hydrolysis time did not result in isomerization of the remaining  $\beta,\gamma$ -unsaturated ketone, indicating an equilibrium mixture of the two ketones.

Examination of molecular models of the  $\alpha,\beta$ -unsaturated ketone indicated the thermodynamically most favored compound should be ketone 89b. Hydrogenation of 89b should take place from the bottom side because of a stereochemical preference for addition of hydrogen from that side<sup>104</sup>. Thus the major product expected from hydrogenation was the cis-fused decalone with the trans-fused decalone as a minor product. The hydrogenation<sup>103,104</sup> was carried out using 5% Pd/C in ethanol containing a small amount of hydrochloric acid. The infrared spectrum ( $\text{CCl}_4$ ) of the resulting ketone ( $1720\text{ cm}^{-1}$ ) was identical



with the ketone obtained from alcohol 85a. A gas chromatographic comparison showed these two ketones to have identical retention times. The stereochemistry of the ketone should be as shown in 90. A minor product of the hydrogenation, detected by gas chromatography, was shown to have an identical retention time with that of the trans-fused decalone 91.

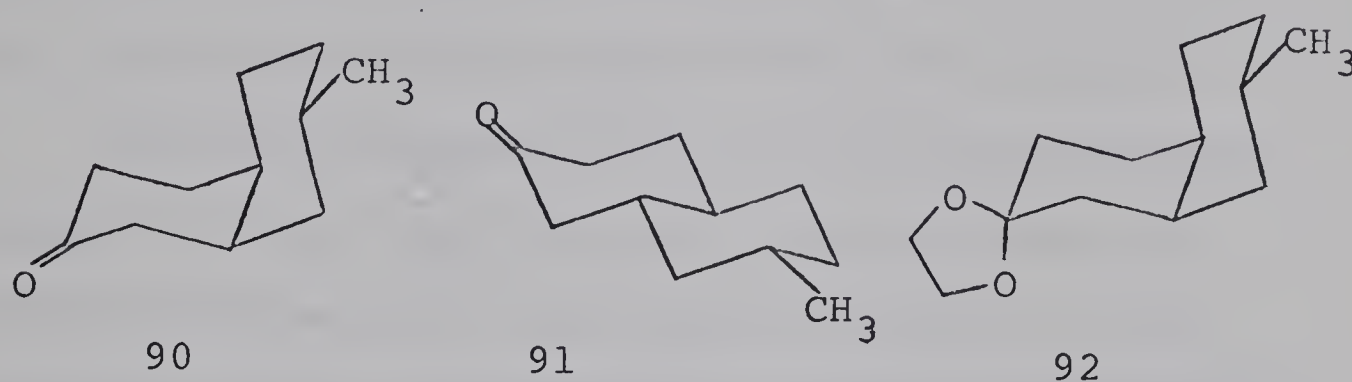
The trans-fused decalone 91 was prepared by lithium-ammonia reduction<sup>103</sup> of the  $\alpha,\beta$ -unsaturated ketone 89. The infrared spectrum of the product indicated the ketone had been reduced to the alcohol. Oxidation (Jones' reagent) converted the alcohol back to the ketone.

Purification of ketone 90 was accomplished only with difficulty. Preparative gas chromatography using various columns resulted in poor separation of the major product from the impurities. Elution chromatography on alumina and on silica gel achieved little if any purification as observed by gas chromatography. Semicarbazone formation<sup>105</sup> followed by regeneration of the ketone also achieved little purification. Purification of a small amount of the ketone 90 was achieved by tedious small scale gas chromatography. The nmr spectrum of the ketone 90 showed a doublet at  $\tau 9.09$  ( $J=5$  cps) and the ir



spectrum showed absorption at  $1710\text{ cm}^{-1}$ . The semicarbazone, prepared from the pure ketone and recrystallized from ethanol-water, had mp  $193\text{--}195^\circ$ .

Since the ketone was very difficult to purify on a large scale, it was transformed to the ethylene ketal 92. It was possible to purify the ketal by preparative glc.



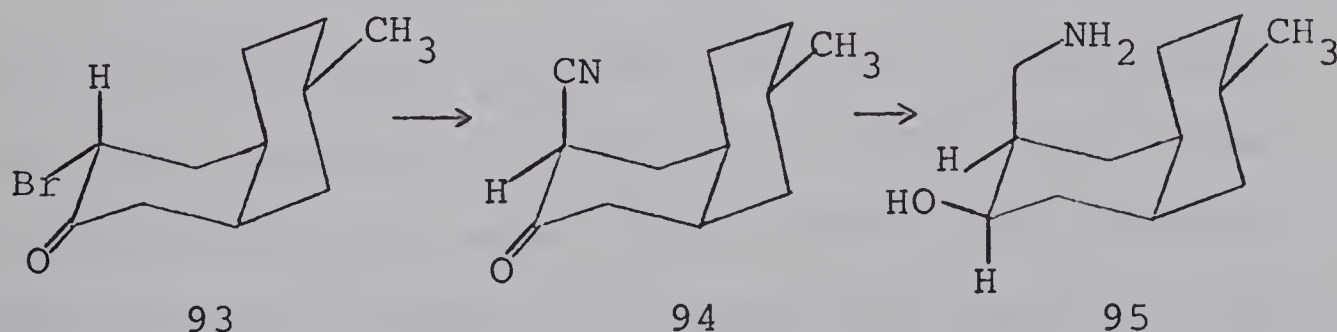
The next step in the synthesis involved bromination of the ketal followed by displacement of the bromine with a cyano group. Bromination of the ketal<sup>106</sup> was carried out in anhydrous ether using an equimolar amount of  $\text{Br}_2$ . After addition was complete the HBr formed in the reaction was neutralized. The product of the bromination contained several components (tlc). After purification by chromatography over alumina a 1:2 mixture of two products was obtained. A mass spectrum as well as a gas chromatographic comparison of the partly purified product indicated that some unbrominated ketal was still present. The mass spectrum showed





a peak at  $m/e$  210 corresponding to ketal as well as one at  $m/e$  289 corresponding to monobromo ketal. Further indication that bromination had occurred was obtained from the nmr spectrum which showed a multiplet at  $\tau$ 6.0 corresponding to a proton geminal to a bromine atom. Because of the impure nature of the reaction product and the difficulties encountered in purification, this approach was not pursued.

The bromination of ketone 90 was next investigated. It was hoped that the  $\alpha$ -bromo ketone 93 could be obtained,<sup>117</sup> the bromine displaced with cyanide and the  $\alpha$ -cyanoketone 94 reduced immediately to 95 before epimerization to the more stable equatorial epimer.



The bromination of ketone 90 using an equimolar amount of  $\text{Br}_2$  in acetic acid resulted in a mixture of compounds absorbing in the infrared<sup>88,116</sup> ( $\text{CCl}_4$ ) strongly at  $1730\text{ cm}^{-1}$ , typical of an equatorial bromo ketone and less strongly at  $1760$  and  $1725\text{ cm}^{-1}$ , typical of a di-equatorial brominated ketone and





another equatorial brominated ketone, respectively. On tlc (silica gel) three components were visible. Chromatography on silicic acid did not effect separation of the two less polar components. The third product eluted from the column was essentially one component according to its tlc behavior. However, the infrared spectrum indicated that it was still a mixture ( $1760$ ,  $1730$ ,  $1725\text{ cm}^{-1}$ ).

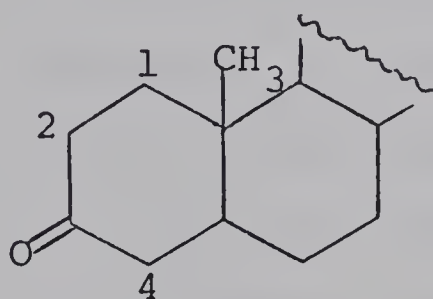
Bromination of the ketone in the presence of a trace of pyridine<sup>108</sup> resulted in the recovery of starting ketone. Bromination in ethanol with pyridinium bromide perbromide<sup>109</sup> resulted in a mixture, the major component of which could not be obtained pure even after chromatography. The complexity of the reaction mixture was not reduced after treating with acetic acid - hydrogen bromide. It was hoped that the reaction product might equilibrate to the thermodynamically more stable desired bromo ketone. The treatment seemed to increase the amount of  $1760$  and  $1725\text{ cm}^{-1}$  carbonyl absorption at the expense of the  $1730\text{ cm}^{-1}$  carbonyl absorption.

Using an impure sample of bromo ketone, obtained from a bromination in acetic acid followed by a chromatographic purification on silicic acid, displacement with cyanide was attempted. The ketone,



dissolved in dimethylformamide, was stirred at room temperature with an excess of sodium cyanide. The infrared spectrum ( $\text{CCl}_4$ ) of the product did not show nitrile absorption. More vigorous treatment with cyanide also did not lead to displacement, presumably because of the hindered nature of the group to be displaced.

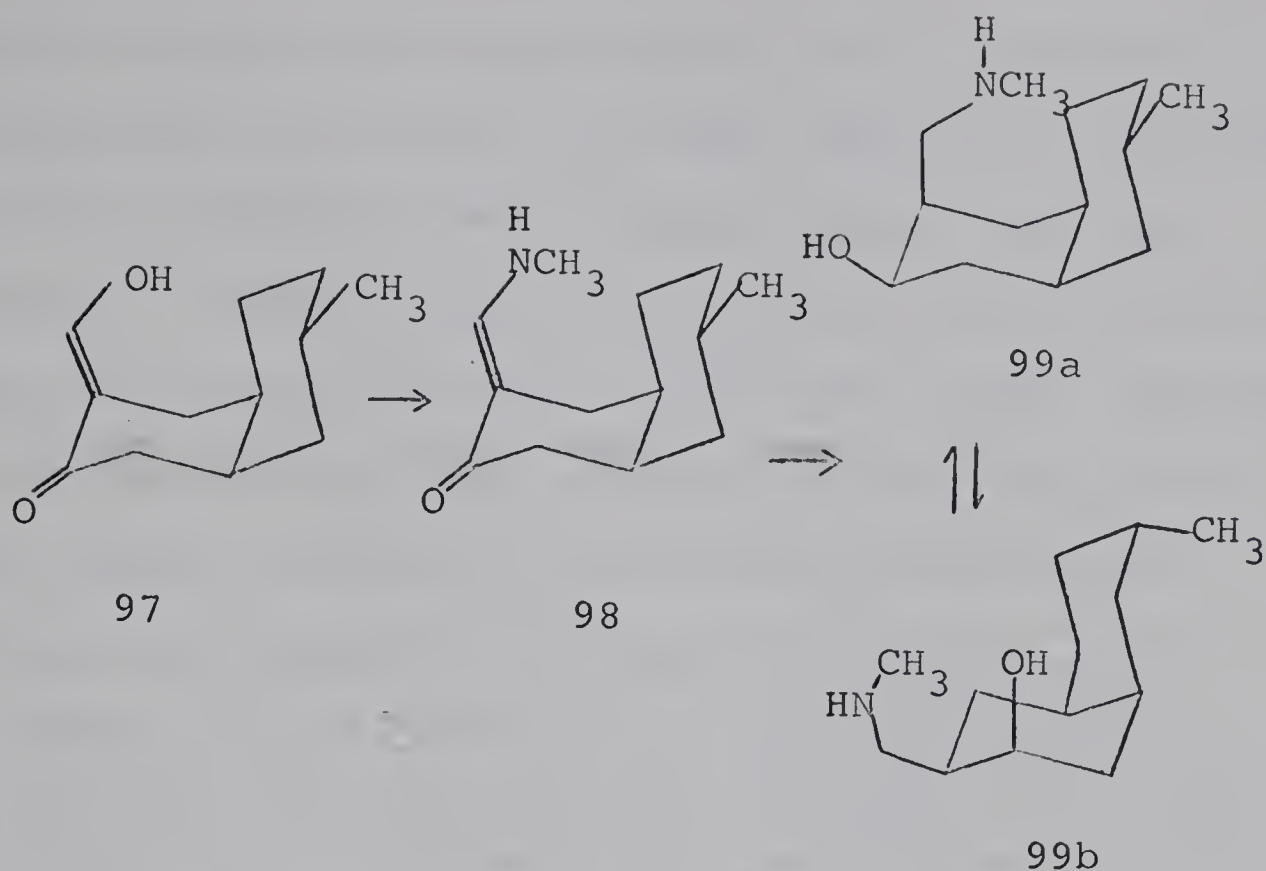
A new approach to the attachment of the amino-methyl group necessary for the construction of the third ring made use of the fact observed by Clinton<sup>118</sup> that A/B - cis 3-keto steroids 96 generally give a preponderance of the 2-hydroxymethylene derivatives. The projected scheme involved the formation of the



96

hydroxymethylene derivative 97, reaction with methyl amine to form 98, and hydrogenation to give the amino alcohol 99. It was expected that catalytic reduction would occur from the convex side of the cis-decalin system to give 99.





The hydroxymethylene derivative 97 was prepared<sup>110</sup> in 88% yield. An infrared spectrum on the crude material showed absorption at 1650 and 1590  $\text{cm}^{-1}$ . The nmr spectrum ( $\text{CCl}_4$ ) on the crude material showed two low field signals at  $\tau$ 1.31 and 1.43 in the ratio 1:4 integrating for one proton based on the integration of the secondary methyl at  $\tau$ 9.1 ( $J=5$  cps) as being equivalent to three protons. The low field signals disappeared when the sample was shaken with  $\text{D}_2\text{O}$  indicating that they are attributable to the hydroxyl proton. A mass spectrum of the material indicated the expected molecular ion at  $m/e$  194(46).

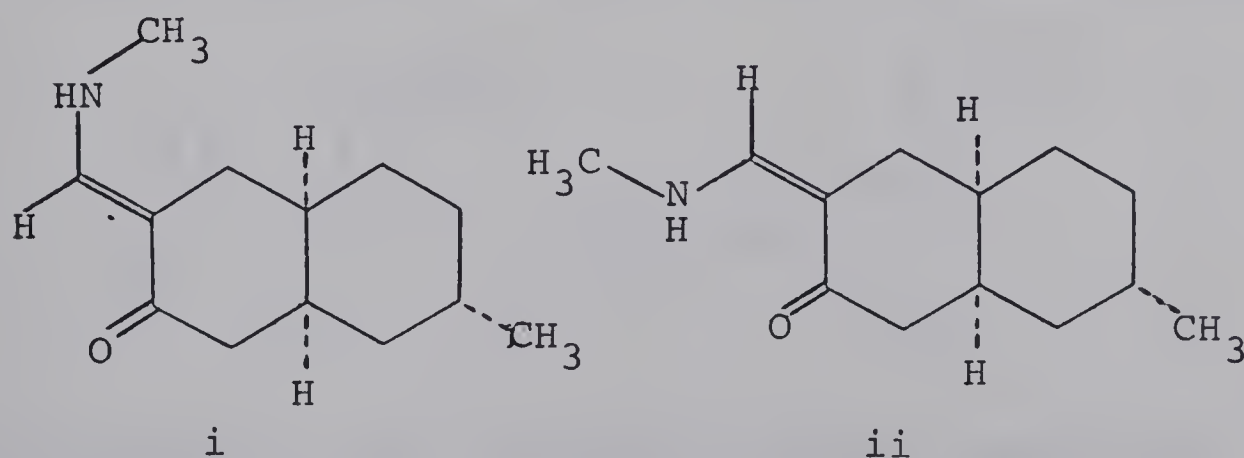
The enamino ketone 98 was prepared by addition



of the  $\alpha$ -hydroxymethylene ketone to a solution of methylamine in benzene. The nmr spectrum on the crude product indicated that a complex mixture had been formed. Partial purification was achieved by filtering the material through a silica gel column, however, four signals were still present\* in the  $\text{N-CH}_3$  region. The enamine could not be purified by distillation.

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\* The nmr spectrum on the purified enamino ketone showed a broad band in the  $\text{N-CH}_3$  region indicating that the amino hydrogen was exchanging at an appreciable rate. Treatment with methylamine in benzene gave a sample whose nmr spectrum showed the  $\text{NH-CH}_3$  coupling. Apparently catalytic amounts of acid from the silica gel chromatography promoted the exchange. The four signals may be attributed to two doublets, one from each of the geometrical isomers i and ii.

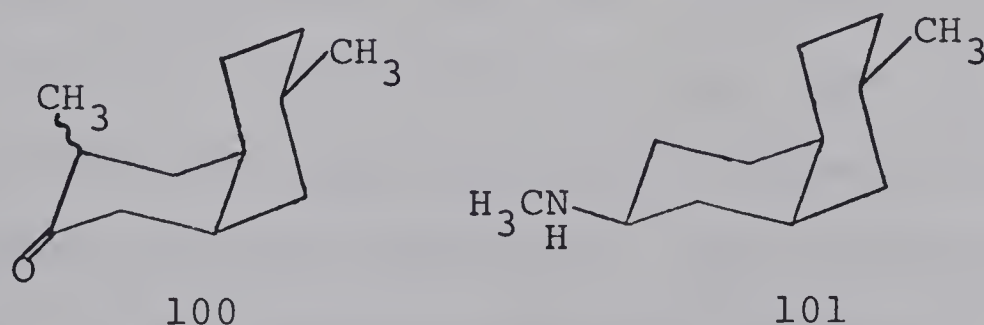






The enamino ketone showed the expected molecular ion at  $m/e$  207(100) with composition  $C_{13}H_{21}NO$  and the ultraviolet spectrum showed a maximum at 327  $m\mu$  in agreement with an  $\alpha,\beta$ -unsaturated ketone with an amino substituent in the  $\beta$  position.

Hydrogenation of the enamino ketone 98 was carried out in ethanol at room temperature and atmospheric pressure using 5% Pd/C as catalyst and proceeded at a very slow rate. Chromatography of the crude hydrogenation product yielded three products. The first was a neutral material, obtained in 26% yield, and tentatively identified as the  $\alpha$ -methyl ketone 100. The infrared spectrum ( $CCl_4$ ) showed no NH or OH absorption but did show strong absorption at  $1720\text{ cm}^{-1}$ . The mass spectrum showed a molecular ion  $m/e$  180(84) in accordance with 100. The second component isolated from the chromatography

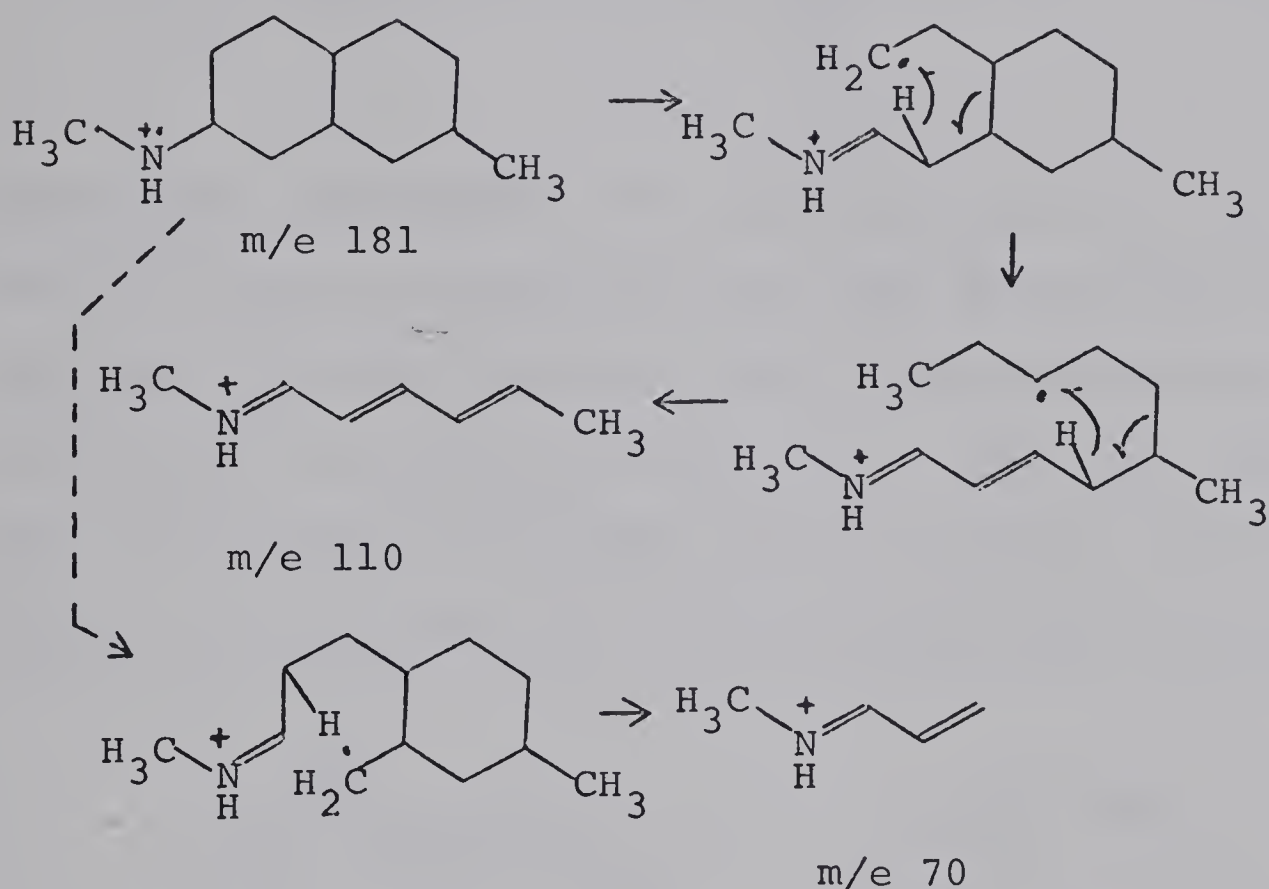


in approximately 25% yield was an amine, tentatively identified as 101 on the basis of its mass spectrum (Scheme 21), which showed a molecular ion at  $m/e$  181(24)



with the composition  $C_{12}H_{23}N$  and major fragments at  $m/e$  110(23) and 70(100).

SCHEME 21

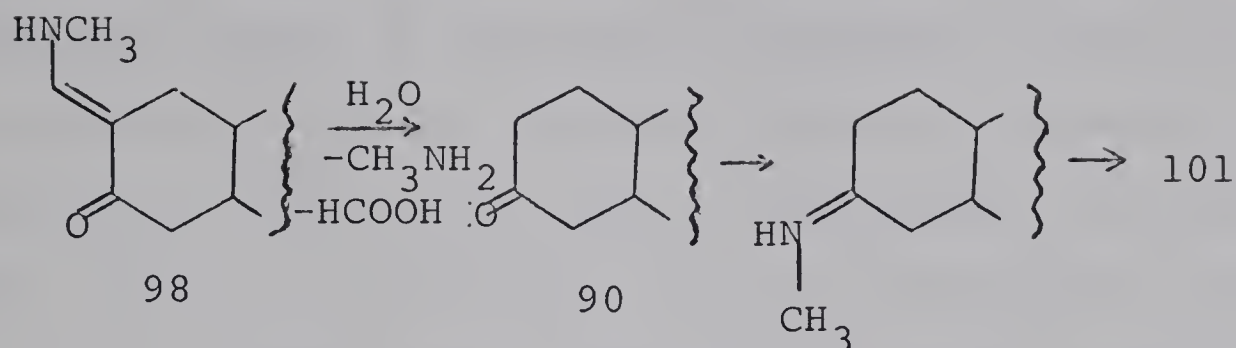


Acetylation yielded a compound which showed absorption in the infrared at  $1650\text{ cm}^{-1}$  typical of an N-acetyl group. The formation of the amine 101 presumably takes place via hydrolytic cleavage of the methylaminomethylene substituent, then reductive amination of the ketone as shown in Scheme 22.

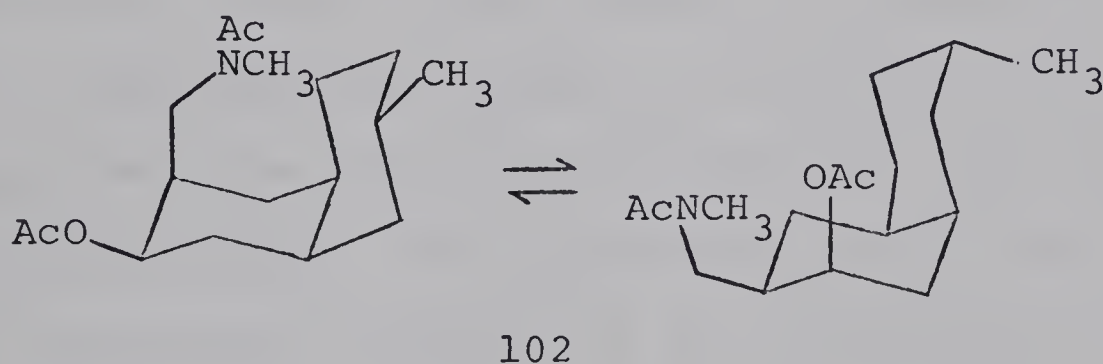
The third, very polar, component was obtained in approximately 25% yield. The infrared spectrum ( $CCl_4$ ) showed absorption at  $3300\text{ cm}^{-1}$  and no carbonyl



## SCHEME 22



absorption. The results of the acetylation of this material led us to believe it was the amino alcohol 99 since the infrared spectrum (CCl<sub>4</sub>) showed absorption at 1740 cm<sup>-1</sup> as well as at 1650 cm<sup>-1</sup>. The mass spectrum of the acetylated amino alcohol\* showed a molecular ion at m/e 295(22) with the composition C<sub>17</sub>H<sub>29</sub>NO<sub>3</sub>



in agreement with structure 102.

The nmr spectrum (CCl<sub>4</sub>) of 102 showed two sets of doublets centered at  $\tau$ 9.1.

The hydrogenation of the enamine ketone 98 was attempted using PtO<sub>2</sub><sup>111</sup>, 5% Rh/Al<sub>2</sub>O<sub>3</sub><sup>112</sup>, 5% Ru/C,

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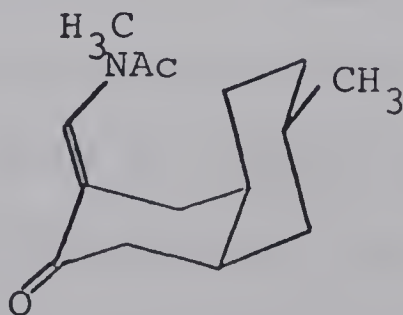
\* The amino alcohol did not show a molecular ion in its mass spectrum.



and 30% Pd/C as catalysts as well as 5% Pd/C for various lengths of time and at pressures ranging up to 2200 psi. In all cases the reaction proceeded no better than with 5% Pd/C at atmospheric pressure. When ethanol containing a trace of hydrochloric acid was used as the solvent the major product was the  $\alpha$ -methyl ketone 100.

Attempted reduction of the enamino ketone 98 with  $\text{NaBH}_4$  gave back starting material. Reduction with  $\text{LiAlH}_4$  gave a hydroxyamine in about 35% yield. The infrared spectrum of the O,N-diacetyl derivative (mol wt 295) was similar to but not identical with the acetylated product from catalytic hydrogenation. Since it was felt that the product of catalytic hydrogenation should have the desired stereochemistry, the hydride reduction product, the stereochemistry of which could not be assigned readily, was not investigated further.

The infrared spectrum of the O-acetylated product, obtained from hydrogenation and hydride reduction of the acetylated enamino ketone 103, was again similar but not identical with the product 102.

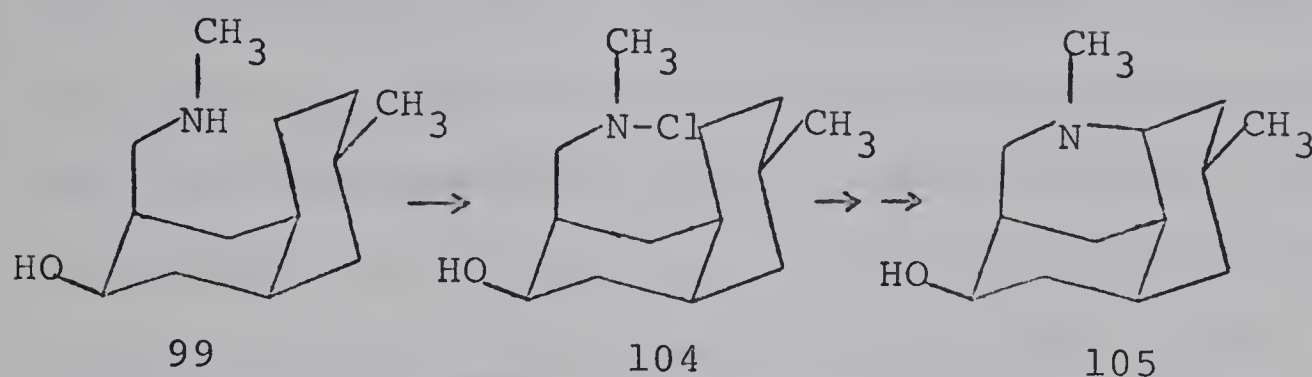


103





At this point we decided to attempt the ring closure of the amino alcohol 99 via photolysis of the corresponding N-chloro compound (Hofmann-Löffler-Freytag reaction).



The N-chloro compound 104 was formed by reacting the amine 99 with N-chlorosuccinimide<sup>113a,b</sup>. Work up of the reaction mixture gave a material which, after distillation analyzed for 11.7% chlorine (expected for 104, 14.3% chlorine). The N-chloro compound was also prepared by using an aq sodium hypochlorite solution<sup>114</sup>. The distilled product in this case showed 13.0% chlorine. Attempts at further purification and characterization were unsuccessful and it was decided to proceed directly with the crude product.

The ring closure<sup>114,115</sup> was attempted by irradiating a solution of the N-chloro amine in trifluoroacetic acid with an ultraviolet source. After irradiation, evaporation of most of the solvent



gave a residual oil, which was treated with methanolic KOH. Chromatography of the product failed to yield any of the desired dihydroluciduline (105), and the mass spectra of the various fractions did not suggest the presence of any of the desired product. Since the structure and stereochemistry of the amino alcohol and the corresponding N-chloro compound had not been established beyond question it was felt that it was necessary to establish unambiguously these points before further ring closures were attempted.

At this time, the structure of luciduline was confirmed in these laboratories by an X-ray crystallographic study on the p-bromobenzoate of dihydroluciduline (carried out by Dr. N. Masaki). In light of this, the synthetic work was suspended. However, further efforts directed toward the synthesis of luciduline are now in progress in these laboratories.



## EXPERIMENTAL

## SECTION THREE

1.  $\alpha$ -Methyl- $\beta$ - anisoylpropionic acid (78)

A solution of methylsuccinic anhydride (64g, 0.56 mol) in anisole (64g, 0.59 mol) was added dropwise (3 hr) with stirring to a cooled solution of powdered anhydrous  $\text{AlCl}_3$  (175g, 1.32 mol) in nitrobenzene (500 ml). After addition was complete the reaction mixture was stirred at room temperature for 28 hr then poured onto 300 g of ice in 200 ml of 6N HCl. The resulting solution, after being subjected to steam distillation to remove nitrobenzene and unreacted anisole, was cooled. The oily residue solidified, the aqueous supernatant liquid was decanted and the residue digested in warm aq  $\text{Na}_2\text{CO}_3$  solution. The insoluble material was filtered off, the filtrate acidified with conc HCl and the precipitate collected. Recrystallization from ethanol-water (1:3) gave 80g (65%) of brownish-white crystals: mp 138-140°; [lit.<sup>97</sup> mp 144°]; tlc -  $\text{SiO}_2$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 1:1) - homogeneous; ir (Nujol) 1705 (acid C=O), 1675 (ketone C=O), 1597, 1508  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\tau$ -0.55 (m, 1,  $\text{COOH}$ ), 2.1 (d, 2,  $J=9$  cps, aromatic  $\text{CH}$ ), 3.18 (d, 2,  $J=9$  cps, aromatic  $\text{CH}$ ), 6.18



(s, 3,  $\text{OCH}_3$ ), 6.8 (c, 3,  $\text{CH}_2\text{-CH}$ ), 8.73 (m, 3,  $\text{CH}_3\text{-CH}$ ).

2.  $\alpha$ -Methyl- $\gamma$ -(p-methoxyphenyl)butyric acid (79)

A mixture of mossy zinc (160g), mercuric chloride (16g), conc HCl (8 ml) and  $\text{H}_2\text{O}$  (240 ml) was shaken for 5 min, then the aqueous solution decanted. To the amalgamated zinc was added  $\text{H}_2\text{O}$  (120 ml), conc HCl (160 ml) and the keto acid 78 (80g, 0.26 mol). The mixture was heated under reflux for 17 hr after which time a further 120 ml of conc HCl was added followed by an additional 3 hr of refluxing. The cooled reaction mixture was filtered, extracted thoroughly with ether, the ether washed with  $\text{H}_2\text{O}$ , then dried ( $\text{MgSO}_4$ ). After filtration, the filtrate was evaporated under reduced pressure and the residue distilled giving 62g (82%) of the acid 79: bp  $185\text{-}186^\circ$  (0.1 mm) [lit.<sup>97</sup> bp  $180\text{-}182^\circ$  (5 mm)]; tlc -  $\text{SiO}_2$  ( $\text{CHCl}_3\text{-CH}_3\text{OH}$ , 3:1) - homogeneous; nmr ( $\text{CDCl}_3$ )  $\tau$ -1.69 (s, 1,  $\text{COOH}$ ), 2.97 (d, 2,  $J=9$  cps, aromatic  $\text{CH}$ ), 3.29 (d, 2,  $J=9$  cps, aromatic  $\text{CH}$ ), 6.32 (s, 3,  $\text{OCH}_3$ ), 7.2-8.5 (c, 5,  $\text{CH}_2\text{-CH}_2\text{-CH}$ ), 8.82 (d, 3,  $J=7$  cps,  $\text{CH}_3\text{-CH}$ ); mass spectrum m/e 208(15), 135(10), 134(50), 122(10), 121(100), 91(12), 78(10), 77(12).

3. 1-Keto-2-methyl-7-methoxy-1,2,3,4-tetrahydro-naphthalene (80)

The acid 79 (61g, 0.275 mol) was added to a







mixture of  $P_2O_5$  (210g, 0.68 mol) in 200 ml of benzene (dried over Na) and heated on the steam bath for 17 hr. The benzene solution was decanted, the residue washed with fresh benzene then decomposed with ice, the resulting solution subjected to steam distillation and the distillate extracted with benzene. The combined benzene extracts were extracted with  $H_2O$ , aq  $NaHCO_3$  and then  $H_2O$ , dried ( $MgSO_4$ ), filtered and the filtrate evaporated. Distillation of the residue gave 26.5g (46%) of the ketone 80: bp  $155^\circ$  (4 mm) {lit.<sup>97</sup>  $150-152^\circ$  (5 mm)}; tlc -  $SiO_2$  ( $CHCl_3$ ) - two components; ir ( $CCl_4$ ) 1680 (C=O), 1615, 1495  $cm^{-1}$ ; nmr ( $CCl_4$ )  $\tau$ 2.7 (d, 1,  $J=3$  cps, aromatic  $\underline{CH}$ ), 3.13 (m, 2, aromatic  $\underline{CH}$ ), 6.3 (s, 3,  $OCH_3$ ), 7.1-8.6 (c, 5,  $\underline{CH_2}-\underline{CH}-\underline{CH_2}$ ), 8.85 (d, 3,  $J=6$  cps,  $\underline{CH_3}-CH$ ).

#### 4. 2-Methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (81)

A mixture of mossy zinc (105g), mercuric chloride (10.5g), conc HCl (5.5 ml) and  $H_2O$  (160 ml) was shaken for 5 min, then the aqueous solution decanted. To the amalgamated zinc was added  $H_2O$  (65 ml), conc HCl (105 ml) and ketone 80 (25 g, 0.12 mol). The mixture was heated at reflux for 20 hr with the addition of 50 ml portions of conc HCl after 3 hr and 7 hr. The reaction mixture was worked up as described for 79. Distillation of the



residual oil gave 12g (52%) of the ether 81: bp 135-137° (3 mm) {lit.<sup>97</sup> 114-115° (5 mm)}; tlc -  $\text{SiO}_2(\text{CH}_2\text{Cl}_2\text{-CHCl}_3, 1:2)$  - homogeneous; ir ( $\text{CCl}_4$ ) 1610, 1500  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 3.1-3.7 (c, 3, aromatic  $\text{CH}$ ), 6.4 (s, 3,  $\text{OCH}_3$ ), 7.1-7.8 (c, 4, benzylic protons), 7.8-8.8 (c, 3,  $\text{CH}_2\text{-CH}$ ), 9.0 (d, 3,  $J=6$  cps,  $\text{CH}_3\text{-CH}$ ).

5. 2-Methyl-7-hydroxy-1,2,3,4-tetrahydronaphthalene (82)

A mixture of the ether 81 (1.5g, 0.09 mol), acetic acid (20 ml) and hydrobromic acid (sp gr 1.49, 3 ml) was heated under reflux for 3 hr, cooled, diluted with 150 ml of  $\text{H}_2\text{O}$  and extracted with ether. The combined ether extracts were washed with  $\text{H}_2\text{O}$ , aq  $\text{NaHCO}_3$  and then  $\text{H}_2\text{O}$ , evaporated under reduced pressure and the residue dissolved in  $\text{CH}_3\text{OH}$  (100 ml) and shaken with 15%  $\text{NaOH}$  (200 ml) for 10 min. The basic solution was extracted thoroughly with Skellysolve B, acidified with conc  $\text{HCl}$  and extracted with ether. The dried ( $\text{MgSO}_4$ ), filtered solution, evaporated under reduced pressure, yielded 1.2g (88%) of the naphthol 82: tlc -  $\text{Al}_2\text{O}_3$  and  $\text{SiO}_2$  ( $\text{CHCl}_3\text{-CH}_3\text{OH}, 9:1$ ) - homogeneous; nmr ( $\text{CDCl}_3$ )  $\tau$ 3.0-3.7 (c, 3, aromatic  $\text{CH}$ ) 4.2 (m, 1,  $\text{OH}$ ), 7.1-7.8 (c, 4, benzylic protons), 7.8-8.8 (c, 3,  $\text{CH}_2\text{-CH}$ ), 9.02 (d, 3,  $J=6$  cps,  $\text{CH}_3\text{-CH}$ ).



## 6. Hydrogenation of the Naphthol 82

The naphthol 82 (1.0g, 0.007 mol) dissolved in 80% aq ethanol (20 ml) containing 5% Ru/C (150mg) was hydrogenated at 110° (1600-1700 psi) for 16 hr. The filtered reaction mixture was evaporated under reduced pressure yielding an oil (0.88g) which was chromatographed over alumina (20g, Metal Hydrides Basic Act. Alumina, 50 ml fractions). Three products were obtained.

Alcohol 84b (190mg), which eluted with benzene-ether (1:1) and ether, was purified further by chromatography then sublimed under low vacuum: mp 71.5-73°; tlc -  $\text{Al}_2\text{O}_3$  (benzene) - homogeneous; ir ( $\text{CCl}_4$ ) 3600, 1040 (eq C-O)  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 6.07 (m, 1,  $W/2 = 8$  cps), 6.95-8.95 (c, 15), 9.0 (s, 1,  $\text{OH}$ , not present in  $\text{CCl}_4 + \text{D}_2\text{O}$ ), 9.12 (d, 3,  $J=5$  cps,  $\text{CH}_3\text{-CH}$ ); mass spectrum m/e 150 ( $\text{C}_{11}\text{H}_{18}$ , 63), 135(93), 121(23), 109(28), 108(58), 107(33), 95(51), 94(62), 93(49), 81(60), 79(52), 69(46), 67(71), 55(75), 41(100).

Alcohol 85a (190mg), which eluted with  $\text{CH}_2\text{Cl}_2$  and  $\text{CH}_2\text{Cl}_2\text{-CHCl}_3$  (1:1) was purified further by chromatography and obtained as a semi-crystalline solid: tlc -  $\text{Al}_2\text{O}_3$  (ether) - homogeneous; ir ( $\text{CCl}_4$ ) 3600, 985 (ax C-O)  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 6.07 (m, 1,  $W/2=11$  cps), 7.45 (s, 1,  $\text{OH}$ ), 7.7-8.9 (c, 15), 9.14 (d, 3,  $J=5$  cps,  $\text{CH}_3\text{-CH}$ ); mass spectrum m/e 150 ( $\text{C}_{11}\text{H}_{18}$ , 77), 135(100),





121(23), 109(40), 108(53), 107(30), 95(47), 94(53), 93(52), 81(60), 79(50), 69(40), 67(70), 55(74), 41(98).

Alcohol 83a or 86b (275 mg), which eluted with  $\text{CHCl}_3$ , was purified further by chromatography and obtained as an oil: tlc -  $\text{Al}_2\text{O}_3$  (ether) - homogeneous; ir ( $\text{CCl}_4$ ) 3600, 1040 (eq C-O)  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 6.4 (m,  $W/2=25$  cps), 6.65 (s, 1,  $\text{OH}$ ), 7.8-9.0 (c, 15), 9.12 (superimposed d, 3,  $\text{CH}_3\text{-CH}$ ).

#### 7. Oxidation of Alcohols 84b, 85a, 83a, 86b

Each alcohol (15-20mg) was dissolved in 10 ml of acetone (refluxed over  $\text{KMnO}_4$  -  $\text{CaSO}_4$  and distilled from it) and to each was added dropwise with rapid stirring an excess of chromic acid solution (Stand. Solution: 26.72g of  $\text{CrO}_3$  and 23 ml of  $\text{H}_2\text{SO}_4$  diluted to 100 ml with  $\text{H}_2\text{O}$ ). The reaction mixture was then quenched with 5% aq  $\text{K}_2\text{CO}_3$  solution, extracted with ether, dried ( $\text{MgSO}_4$ ), filtered and the filtrate evaporated yielding ketone: tlc -  $\text{Al}_2\text{O}_3$  (benzene-ether, 1:1) - for each ketone, one major component and traces of less polar impurities; ir ( $\text{CCl}_4$ ) 1720 $\rightarrow$ 1715  $\text{cm}^{-1}$ .

#### 8. 1,4-Dihydro-2-methoxy-7-methyl-5,6,7,8-tetrahydronaphthalene (87)

Into a flask containing the ether 81 (3g, 0.02 mol) dissolved in ether (25 ml) was distilled 100 ml





of  $\ell$ -NH<sub>3</sub>. Lithium ribbon (1.6g) cut up into small pieces was added over a 10 min period, then after a further 10 min absolute ethanol was added until the blue color of the reaction mixture was discharged. The NH<sub>3</sub> was allowed to evaporate, the residue diluted with H<sub>2</sub>O, extracted with Et<sub>2</sub>O and the extract dried (anh K<sub>2</sub>CO<sub>3</sub>), filtered and evaporated under reduced pressure yielding 2.7g (92%) of the Birch reduction product 87: ir (CCl<sub>4</sub>) 3025-2995 (olefinic C-H), 1703 (C=C?), 1673 (enol ether C=C), 1215 (C-O) cm<sup>-1</sup>; nmr (CCl<sub>4</sub>)  $\tau$ 5.55 (t, 1, J=3 cps, olefinic CH), 6.58 (s, 3, OCH<sub>3</sub>), 7.5 (broad s, 4, allylic protons), 7.9-8.7 (c), 9.05 (d, 3, J=5 cps, CH<sub>3</sub>-CH).

#### 9. Ethylene Ketal 88

The enol ether 87 (2g, 0.11 mol), dissolved in 75 ml of benzene containing 2 ml of ethylene glycol and a catalytic amount of p-toluene sulfonic acid was heated under reflux for 13 hr, collecting the azeotroped water. After 5 hr another catalytic amount of p-TsOH was added. After evaporation of the solvent under reduced pressure, the residual oil was diluted with Skellysolve B and extracted with dil NaHCO<sub>3</sub> solution, dried (anh K<sub>2</sub>CO<sub>3</sub>), filtered and the filtrate evaporated. Distillation, followed by



careful fractional distillation yielded analytically pure ketal 88: bp 80-105° (0.05 mm); ir (CCl<sub>4</sub>) 1675 ( $\alpha,\beta$ -unsat. C=O, weak), 1610 (C=C), weak) cm<sup>-1</sup>; nmr (CCl<sub>4</sub>)  $\tau$ 6.2 (s, 4, ketal protons), 7.8-8.8 (c, 13), 9.06 (d, 3, J=5 cps, CH<sub>3</sub>-CH); mass spectrum m/e 208 (C<sub>13</sub>H<sub>20</sub>O<sub>2</sub>, 41), 190(12), 107(7), 99(19), 91(7), 87(15), 86(100).

Anal. Calcd. for C<sub>13</sub>H<sub>20</sub>O<sub>2</sub>: C, 74.96; H, 9.68.  
Found: C, 75.05; H, 9.40.

#### 10. Hydrogenation of the Ethylene Ketal 88

The ketal (210mg) dissolved in 15 ml of 80% aq ethanol containing 5% Ru/C (50mg) was subjected to hydrogenation at 110° (1700 psi) for 16 hr. After filtration and removal of the solvent under reduced pressure 150mg of material was obtained: tlc - Al<sub>2</sub>O<sub>3</sub> (ether) - three products.

The hydrogenation products were refluxed for 2 hr in 95% ethanol (30 ml) containing 10% H<sub>2</sub>SO<sub>4</sub> (3 ml). After neutralizing with aq NaHCO<sub>3</sub> solution, most of the ethanol was removed under reduced pressure and the aqueous mixture extracted with benzene. The dried (MgSO<sub>4</sub>), filtered benzene, after evaporation, yielded an oil which was evaporatively distilled (70-90°, 0.07 mm): ir (CCl<sub>4</sub>) 3600 cm<sup>-1</sup>.



### 11. $\alpha,\beta$ -Unsaturated Ketone 89

The enol ether 87 (4.7g, 0.027 mol), dissolved in methanol (100 ml) containing 3NHCl (70 ml), was heated under reflux for 1.25 hr. The reaction mixture was diluted with  $H_2O$ , extracted with benzene and the benzene extracts washed with 5% aq  $NaHCO_3$ , dried ( $MgSO_4$ ), filtered and the filtrate concentrated under reduced pressure giving 4.4g (100%) of ketone: bp 102-117° (0.8 mm); ir ( $CCl_4$ ) 1725 ( $\beta, \gamma C=O$ , weak), 1680 ( $\alpha, \beta C=O$ ) 1625 ( $C=C$ )  $cm^{-1}$ ; nmr ( $CCl_4$ )  $\tau$ 4.37 (s, 1, olefinic  $\underline{CH}$ ), 7.3-7.9 (c, 15), 9.1 (m, 3,  $\underline{CH}_3-CH$ ).

### 12. Hydrogenation of Ketone 89

The ketone 89 (2.04g, 0.012 mol), dissolved in 95% ethanol (50 ml) containing 5 ml of 3NHCl and 600mg of 5% Pd/C, was subjected to hydrogenation at room temperature and atmospheric pressure until no more uptake of  $H_2$  was observed (20 hr). The catalyst was filtered off, most of the solvent removed under reduced pressure, the residual oil dissolved in ether and the ether extracted with  $H_2O$ . After drying ( $MgSO_4$ ), filtration and evaporation of the filtrate, 1.9g (92%) of ketone 90 was obtained. The ketone was purified by gas chromatography using a 20% QF-1, 12' x  $\frac{3}{8}$ ", 30/60 Chromo W column: ir ( $CCl_4$ ) 1720  $cm^{-1}$ ;





nmr ( $\text{CDCl}_3$ )  $\tau$ 7.35-8.9 (c, 15), 9.09 (d, 3,  $J=5$  cps,  $\text{CH}_3\text{-CH}$ ).

The semicarbazone derivative (mp 193-195°) of the pure ketone was prepared<sup>105a</sup> in the usual manner and recrystallized twice from a 1:2 mixture of ethanol-water: ir (Nujol) 3440-3180 ( $\text{NH}, \text{NH}_2$ ), 1675 (amide I), 1648 ( $\text{C=N}$ ), 1560 (amide II)  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{12}\text{H}_{21}\text{NO}_3$ : C, 64.54; H, 9.48.  
Found: C, 64.56; H, 9.23.

### 13. Reduction of the $\alpha, \beta$ -Unsaturated Ketone 89

The ketone (80mg) dissolved in a 1:1 mixture of dioxane-ether (15 ml) was added dropwise (3 min) with stirring to 15 ml of  $\ell\text{-NH}_3$  to which had been added an excess of Li. After addition was complete,  $\text{NH}_4\text{Cl}$  was added until the blue color of the solution was discharged, the ammonia allowed to evaporate and  $\text{H}_2\text{O}$  added. The aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$ , dried ( $\text{MgSO}_4$ ), filtered and evaporated giving 67mg of material. Distillation at 80-170° (0.07 mm) yielded a semicrystalline solid: ir ( $\text{CCl}_4$ ) 3600  $\text{cm}^{-1}$ .

Oxidation of the alcohol with Jones' reagent in the usual manner gave the trans-fused ketone 91: ir ( $\text{CCl}_4$ ) 1713  $\text{cm}^{-1}$ . The comparison of retention times of this ketone and the minor product from the hydro-





genation of the  $\alpha,\beta$ -unsaturated ketone was carried out on a 16" x  $\frac{1}{4}$ ", 15% Apiazon L on 60/80 Chromo W column.

#### 14. Attempted Purification of Ketone 90 by Semicarbazone Formation

Semicarbazone derivative of the impure ketone was prepared in the usual manner<sup>105a</sup>. The crystals were collected and recrystallized twice from ethanol-water (1:2).

Hydrolysis of the semicarbazone was carried out by heating it at reflux for 1.5 hr in a mixture of Skellysolve B (30 ml) and H<sub>2</sub>O (6 ml) containing 0.7g of oxalic acid. The mixture was then diluted with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried (MgSO<sub>4</sub>), filtered and the filtrate concentrated under reduced pressure yielding ketone 90 which was still impure.

#### 15. Ethylene Ketal 92

The ketone 90 (1.02g, 0.006 mol), dissolved in 50 ml of benzene with ethylene glycol (2.1g, 0.034 mol) and a catalytic amount of p-TsOH added, was heated at reflux for 6 hr, collecting the azeotroped water. Work-up was carried out in a similar manner to that for ketal 88 and yielded 1.28g (98%) of ketal 92. Gas chromatographic purification of the



ketal was carried out on a 20% QF-1, 12" x  $\frac{3}{8}$ ", 30/60 Chromo W column. A 59% yield of pure ketal was obtained, based on the weight of the crude ketal injected into the gas chromatograph: nmr ( $\text{CCl}_4$ )  $\tau$ 6.2 (s, 4, ketal protons), 8.0-9.0 (c, 15), 9.17 (d, 3,  $J=5$  cps,  $\text{CH}_3\text{-CH}$ ).

#### 16. Bromination of Ketal 92

To a solution of the ketal (100mg, 0.0048 mol) dissolved in ether (25 ml) was added dropwise with stirring 1 molar eq of  $\text{Br}_2$  (2.59g/50 ml  $\text{CH}_2\text{Cl}_2$ ) dissolved in  $\text{CH}_2\text{Cl}_2$ . After addition was complete, 1 molar eq of  $\text{NaOCH}_2\text{CH}_2\text{OH}$  (0.5g/7.5 ml  $\text{HOCH}_2\text{CH}_2\text{OH}$ ) dissolved in ethylene glycol was added, the reaction mixture poured into  $\text{H}_2\text{O}$  and extracted with ether. The ether extract was dried ( $\text{MgSO}_4$ ), filtered and the filtrate evaporated under reduced pressure yielding 141mg of product; tlc -  $\text{Al}_2\text{O}_3$  (benzene) - at least four products. Chromatography on alumina (8g, 50 ml fractions) yielded a major product which eluted with Skellysolve B - benzene (1:1): (71mg); tlc -  $\text{Al}_2\text{O}_3$  (benzene) - a 1:2 mixture; ir ( $\text{CCl}_4$ ) 1095 (C-O)  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 5.7-6.3 (m, 2,  $\text{CH-Br}$ ), 6.2 (s, 2, ketal protons), 7.5-8.9 (c, ), 9.13 (m, 3,  $\text{CH}_3\text{-CH}$ ).



17. Bromination of Ketone 90

To the ketone (56mg, 0.0034 mol) dissolved in 1.5 ml of acetic acid was added dropwise with stirring 1 molar eq of  $\text{Br}_2$  dissolved in HOAc. After addition was complete,  $\text{H}_2\text{O}$  was added and extraction with  $\text{CH}_2\text{Cl}_2$  carried out. The methylene chloride extract was dried ( $\text{MgSO}_4$ ), filtered and the filtrate evaporated under reduced pressure yielding 73mg of material which was chromatographed on silicic acid (3g, Mallinkrodt 100 mesh, 20 ml fractions).

Fraction eluted with Skellysolve B - benzene (2:1): 5 mg; tlc -  $\text{SiO}_2$  (benzene) - three components; ir ( $\text{CCl}_4$ ) 1750, 1730, 1720  $\text{cm}^{-1}$ .

Fraction eluted with Skellysolve B - benzene (1:1): 38mg; tlc -  $\text{SiO}_2$  (benzene) - two components; ir ( $\text{CCl}_4$ ) 1760, 1730, 1725  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 5.25 (m, 1,  $\text{CHBr}$ ), 7.2-8.8 (c), 9.0 (m, 3,  $\text{CH}_3\text{-CH}$ ).

Fraction eluted with Skellysolve B - benzene (1:1): 15mg; tlc -  $\text{SiO}_2$  (benzene) - one major, one minor component; ir ( $\text{CCl}_4$ ) 1760, 1730, 1725  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 5.2 - 5.8 (m, 1,  $\text{CH-Br}$ ), 7.2-8.8 (c), 9.01 (d, 3,  $J=5$  cps,  $\text{CH}_3\text{-CH}$ ).

18.  $\alpha$ -Hydroxymethylene Ketone 97

To a suspension of freshly prepared  $\text{NaOCH}_3$  (15g, 0.65 mol Na, 250 ml  $\text{CH}_3\text{OH}$ ; excess solvent



evaporated to dryness under reduced pressure) in dry benzene (250 ml) under an  $N_2$  atmosphere was added ethyl formate (115 ml, 156g, 2.1 mol). The reaction mixture was stirred for 0.5 hr then cooled in ice and the ketone (40g, 0.24 mol) added dropwise over a 1 hr period, after which it was allowed to warm to room temperature and stirred for a further 18 hrs. The reaction mixture was diluted with benzene and extracted with dil HCl. The combined benzene extracts were extracted with 2% aq KOH solution at 7° (cold room). The basic extracts, acidified with dil HCl, were extracted with benzene-ether, the combined extracts of which were washed with  $H_2O$ , dried ( $MgSO_4$ ), filtered and the filtrate evaporated under reduced pressure yielding 40g (88%) of  $\alpha$ -hydroxymethylene ketone 97: tlc -  $SiO_2$  (benzene-ether, 1:1) - one component with a trace of a polar impurity; ir ( $CCl_4$ ) 1710 (weak, ketone C=O), 1650 (enol C=C), 1590  $cm^{-1}$ ; nmr ( $CCl_4$ )  $\tau$  1.31, 1.43 (two s, 1,  $OH$ , not observed in  $CCl_4 + D_2O$ ), 7.2-8.9 (c, 13), 9.1 (d, 3,  $J=5$  cps,  $CH_3-CH$ ); mass spectrum m/e 194(40), 166(15), 148(17), 137(44), 133(17), 119(29), 109(40), 95(82), 81(81), 70(40), 67(63), 55(97), 41(100).







### 19. Enamino Ketone 98

The  $\alpha$ -hydroxymethylene ketone 97 (40g, 0.21 mol), dissolved in 100 ml of dry benzene, was added dropwise over a 1 hr period to a cooled benzene solution containing anhydrous  $\text{CH}_3\text{NH}_2$  (25g). During the addition methyl amine was bubbled slowly through the reaction mixture. After addition was complete stirring was continued at room temperature for 15 hr, then the solvent was evaporated under reduced pressure yielding approximately 40g (92%) of crude enamino ketone 98: tlc -  $\text{SiO}_2$  ( $\text{CHCl}_3$ - $\text{CH}_3\text{OH}$ , 19:1) - two major, four minor components; ir ( $\text{CCl}_4$ ) 3500-3100 (NH), 1720 (weak), 1650 (C=O), 1575 (C=C)  $\text{cm}^{-1}$ . The crude enamino ketone (1g) was purified by filtering it through a column of silica gel (30g) using  $\text{CHCl}_3$  as eluent: uv max (EtOH) 327 m $\mu$  ( $\epsilon$ 19000); nmr ( $\text{CCl}_4$ ) (sample treated with  $\text{CH}_3\text{NH}_2$  in benzene after purification)  $\tau$ -0.1 (m, 1,  $\text{NH}$ , not obs in  $\text{CCl}_4$  +  $\text{D}_2\text{O}$ ), 1.13 (s, <1), 3.6 (d, 1,  $J=13$  cps, olefinic  $\text{CH}$ ; in  $\text{CCl}_4$  +  $\text{D}_2\text{O}$ , 3.63, s, 1), 6.92-7.2 (four signal c, 3,  $\text{CH}_3$ -NH; in  $\text{CCl}_4$  +  $\text{D}_2\text{O}$ , 7.07, s, 3 and 7.15, s, 1); mass spectrum m/e 207 ( $\text{C}_{13}\text{H}_{21}\text{NO}$ , 100), 192(13), 166(19), 150(63), 136(17), 122(28), 111(39), 95(28), 83(37), 70(51).

### 20. Hydrogenation of the Enamino Ketone 98

Freshly purified enamino ketone (13g), evaporatively



distilled (130-180°, 0.08 mm) yielding 7.5g (distilled in 1g quantities), was dissolved in 95% ethanol (50 ml) and subjected to hydrogenation in the presence of 5% Pd/C (0.5g) at room temperature and atmospheric pressure for 72 hr. Fresh 0.5g portions of catalyst were added after 12 and 36 hr. The residual oil, after filtration and evaporation of the solvent under reduced pressure, was chromatographed on alumina (250g, Metal Hydrides Activated Neutral Alumina, 200 ml fractions).

Fraction eluted with benzene (100): 2g; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3$ ) - neutral, homogeneous; ir ( $\text{CCl}_4$ ) 1720  $\text{cm}^{-1}$ ; mass spectrum m/e 180(84), 152(37), 136(100), 109(50), 95(97), 81(76).

Fraction eluted with  $\text{Et}_2\text{O}-\text{CH}_2\text{Cl}_2$  (1:1) and  $\text{CHCl}_3-\text{CH}_3\text{OH}$  (19:1) (101): 0.8g; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3-\text{CH}_3\text{OH}$ , 19:1) - one major basic component; ir ( $\text{CCl}_4$ ) 3300  $\text{cm}^{-1}$ ; mass spectrum m/e 181( $\text{C}_{12}\text{H}_{23}\text{N}$ , 24), 150(8), 110(23), 96(17), 71(7), 70(100). Acetylation of the amine was carried out under the usual conditions for 16 hr: ir ( $\text{CCl}_4$ ) 1650  $\text{cm}^{-1}$ .

Fraction eluted with  $\text{CHCl}_3-\text{CH}_3\text{OH}$  (9:1) (99): 2.0g; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CHCl}_3-\text{CH}_3\text{OH}$ , 19:1) - one major component: ir ( $\text{CCl}_4$ ) 3450, 3300 (NH,OH)  $\text{cm}^{-1}$ .

Acetylation was carried out under the usual conditions,



3.5 hr: ir ( $\text{CCl}_4$ ) 1740 (OAc), 1650 (Nac)  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 5.66-6.3 (m, 1,  $\text{CH-O}$ ), 5.98 (d, 1,  $J=8$  cps,?), 7.13 (s, 3,  $\text{CH}_3\text{-N}$ ), 6.9-7.9 (c, 2,  $\text{CH}_2\text{-N}$ ), 8.02 (s, 6,  $\text{CH}_3\text{-C=O}$ ), 8.15-8.9 (c), 9.1 (m, 3,  $\text{CH}_3\text{-CH}$ ); mass spectrum m/e 295 ( $\text{C}_{17}\text{H}_{29}\text{NO}_3$ , 22), 252(22), 236(22), 235(64), 222(22), 220(39), 162(46), 152(34), 149(23), 138(30), 110(32), 106(24), 98(30), 96(35), 74(100).

## 21. $\text{LiAlH}_4$ Reduction of the Enamino Ketone 98

The enamino ketone (240mg), dissolved in 50 ml of ether, was stirred at room temperature for 16 hr with an excess of  $\text{LiAlH}_4$  (150mg). The work-up of the reaction mixture in the usual manner<sup>119</sup> yielded 210mg (86%) of amino alcohol which was chromatographed on alumina. The fraction eluted with  $\text{CHCl}_3\text{-CH}_3\text{OH}$  (99:1 to 98:2) was acetylated with acetic anhydride-pyridine (1:2): ir ( $\text{CCl}_4$ ) 1740 (OAc), 1650 (Nac)  $\text{cm}^{-1}$ .

## 22. N-Acetyl Enamino Ketone 103

Purified enamino ketone (1.0g, 0.005 mol), dissolved in 3 ml of acetic anhydride-pyridine (1:2), was acetylated at room temperature for 12 hr. The product was chromatographed on alumina (30g, 150 ml fractions). Fractions eluted with benzene-ether (1:1) and  $\text{CHCl}_3$ : 440mg, 37%; tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CH}_2\text{Cl}_2\text{-CHCl}_3$ , 1:1) - homogeneous; ir ( $\text{CCl}_4$ ) 1680 (C=O), 1650 (Nac),





1575  $\text{cm}^{-1}$ ; uv max (EtOH) 322 ( $\epsilon$  3900), 290  $\text{m}\mu$  ( $\epsilon$  2860);  
 nmr ( $\text{CCl}_4$ )  $\tau$ 2.63 (m, 1, olefinic), 6.8-7.2 (five  
 signal c, 3,  $\text{CH}_3\text{-N}$ ), 7.87-7.9 (two s, 3,  $\text{CH}_3\text{-C=O}$ ),  
 7.6-8.9 (c), 9.1 (m, 3,  $\text{CH}_3\text{-CH}$ ); mass spectrum m/e  
 249(4), 221(52), 220(34), 207(70), 206(41), 150(54),  
 148(34), 111(34).

### 23. Hydrogenation of the N-Acetyl Enamino Ketone 103

The N-acetylated enamino ketone (390mg, 0.0016 mol),  
 dissolved in 10 ml of 95% ethanol containing 5% Pd/C  
 (100mg), was subjected to hydrogenation at room tempera-  
 ture and atmospheric pressure for 8 hr. The catalyst  
 was filtered off, the solvent evaporated under re-  
 duced pressure and the residue evaporatively dis-  
 tilled (150-180°, 0.04 mm): tlc -  $\text{Al}_2\text{O}_3$  ( $\text{CH}_2\text{Cl}_2\text{-CHCl}_3$ ,  
 1:1) - one major, one minor component; ir ( $\text{CCl}_4$ ) 1715  
 ( $\text{C=O}$ ), 1650 (NAc)  $\text{cm}^{-1}$ ; mass spectrum m/e 251(12),  
 178(44), 150(36), 135(60), 109(23), 108(26), 107(27),  
 95(100), 94(45), 93(45), 86(25), 81(35), 79(46), 73(75).

### 24. $\text{NaBH}_4$ Reduction of the N-Acetyl Amino Ketone

A mixture of N-acetyl amino ketone (690mg, 0.0028  
 mol) and  $\text{NaBH}_4$  (300mg) in 95% ethanol (25 ml) was  
 stirred at room temperature for 3 hr, then diluted  
 with  $\text{H}_2\text{O}$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The dried ( $\text{MgSO}_4$ )  
 and filtered extract, after evaporation of the solvent





under reduced pressure yielded 670mg (96%) of amino alcohol which was chromatographed on alumina three successive times before a homogeneous product (184mg) was obtained: tlc -  $\text{Al}_2\text{O}_3(\text{CHCl}_3)$ ; ir ( $\text{CCl}_4$ ) 3400, 1640 (N-Ac)  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\tau$ 5.7 (m, 1,  $\text{CH-O}$ ), 6.1 (m, 1), 6.2 (m, 1), 6.6-7.2 (c, 2-3,  $\text{CH}_2\text{-N}$ ), 6.93 (s, 3,  $\text{CH}_3\text{-N}$ ), 7.95 (s, 3,  $\text{CH}_3\text{-C=O}$ ), 8.1-8.9 (c, 14-15), 9.1 (m, 3,  $\text{CH}_3\text{-CH}$ ).

#### 25. Acetylation of the N-Acetyl Amino Alcohol

The alcohol (23mg), was acetylated under the usual conditions for 14 hr. The product, chromatographed on alumina (2g, 20 ml fractions), eluted with  $\text{Et}_2\text{O-CH}_2\text{Cl}_2$  (1:1) to  $\text{CH}_2\text{Cl}_2$ : tlc -  $\text{Al}_2\text{O}_3(\text{CHCl}_3)$  - homogeneous; ir ( $\text{CCl}_4$ ) 1735, 1650  $\text{cm}^{-1}$ ; mass spectrum m/e 295(14), 252(15), 235(31), 192(8), 162(25), 87(26), 86(100), 74(26).

#### 26. N-Chloro Amino Alcohol 104

a. To partially purified (one chromatography on the crude hydrogenation product of the enamino ketone 98) amino alcohol 99 (0.5g, 0.0024 mol) dissolved in ether (25 ml) was added N-chlorosuccinimide (0.4g, 0.003 mol). The mixture was stirred under  $\text{N}_2$  for 42 hr, diluted with  $\text{H}_2\text{O}$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, the



filtrate evaporated and the residual oil evaporatively distilled yielding a viscous product which was collected between 200-260° (0.02 mm):

Anal. Calcd. for  $C_{13}H_{24}NOCl$ : Cl, 14.3% Found: Cl, 11.7%.

b. To partially purified amino alcohol 99 (0.6g, 0.0028 mol) dissolved in  $CH_2Cl_2$  (20 ml) was added excess aq NaOCl solution. The mixture was stirred vigorously for 40 min at room temperature, the aqueous layer decanted, fresh NaOCl solution added and stirred for another 40 min. The reaction mixture was then extracted with  $H_2O$ , the methylene chloride dried ( $MgSO_4$ ), filtered and the filtrate evaporated to an oil (0.73g) which was evaporatively distilled (150-230°, 0.03 mm).

Anal. Calcd. for  $C_{13}H_{24}NOCl$ : Cl, 14.3%. Found: Cl, 13.0%.

## 27. Attempted Hofmann-Löffler-Freytag Reaction

The N-chloroamine (0.2g, 0.0082 mol), obtained from the chlorination using NaOCl, was dissolved in 2 ml of trifluoroacetic acid in a quartz cell. The solution was purged by bubbling  $N_2$  through it, then irradiated at 15-20° for 24 hr using a medium pressure ultraviolet source (Hanovia Type A, 673A, 550W).



The solvent was evaporated under reduced pressure, methanolic KOH (0.5g/6 ml) added and the mixture refluxed for 1 hr. The solvent was evaporated,  $H_2O$  added and the aqueous solution extracted with  $CHCl_3$ . The combined  $CHCl_3$  extracts were dried ( $Na_2SO_4$ ), filtered and the filtrate evaporated giving a residue which was chromatographed on alumina (3g, 20 ml fractions). An examination of the fractions using tlc, ir and mass spectrometry indicated none of the desired dihydroluciduline.



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